Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

OCTOBER, 1958
Volume 8 — Number 10

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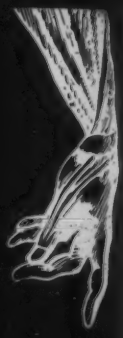

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Whiplash injury	3	2	1	—	—
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STUDY 3[3]					
Herniated disc	8	6	2	—	—
Acute fibromyositis	8	8	—	—	—
Torticollis	1	—	—	1	—
		"significant"			
STUDY 4[6]					
Pyramidal tract and acute myalgic disorders	30	27	—	2	1
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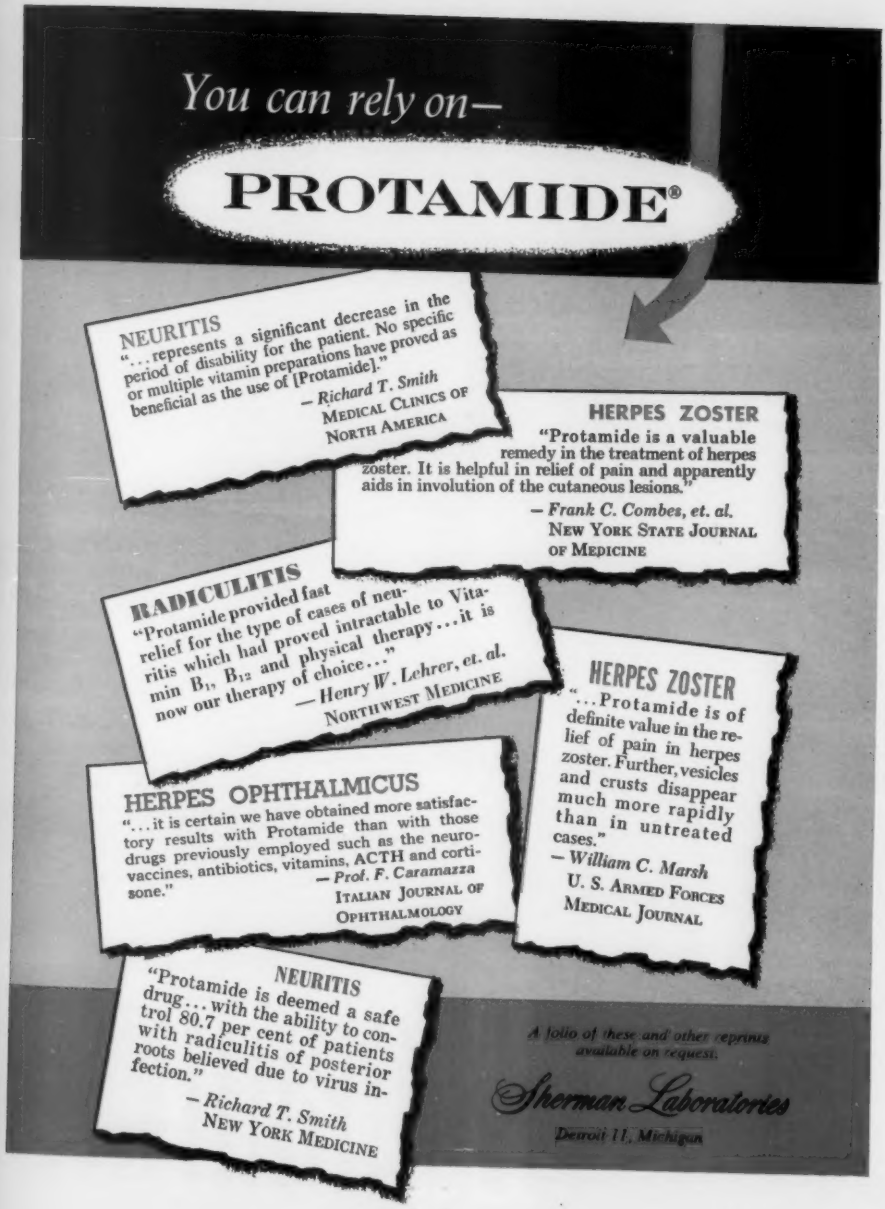
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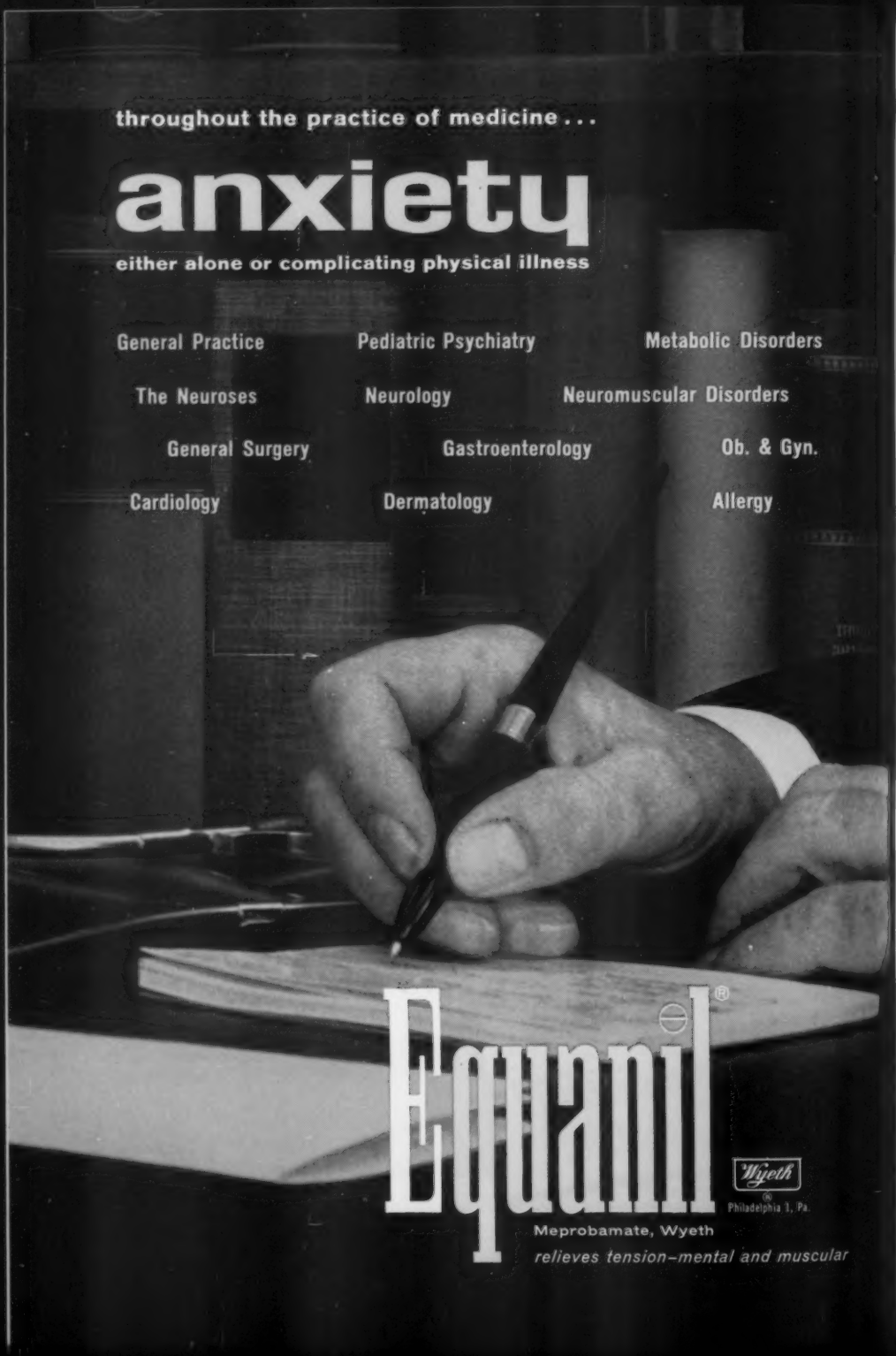
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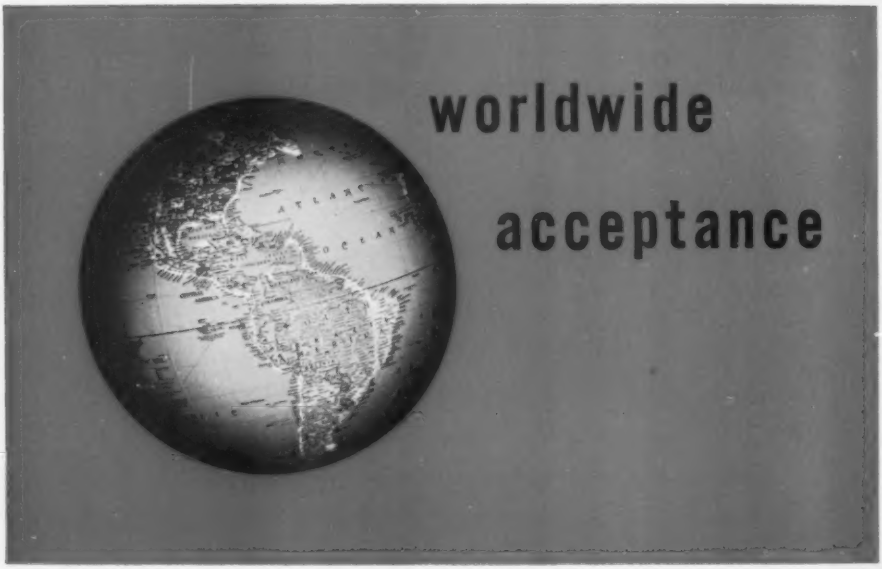

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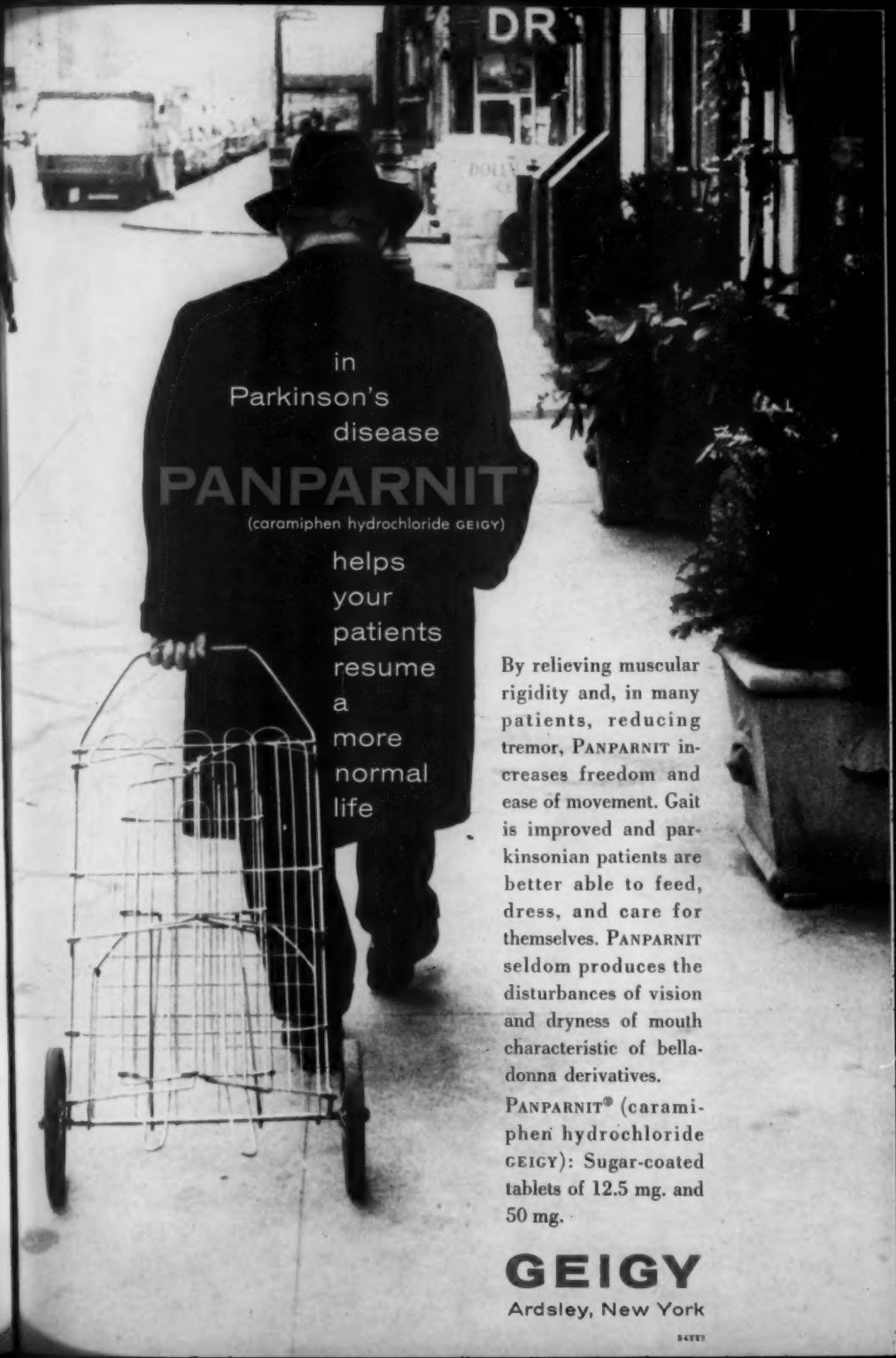

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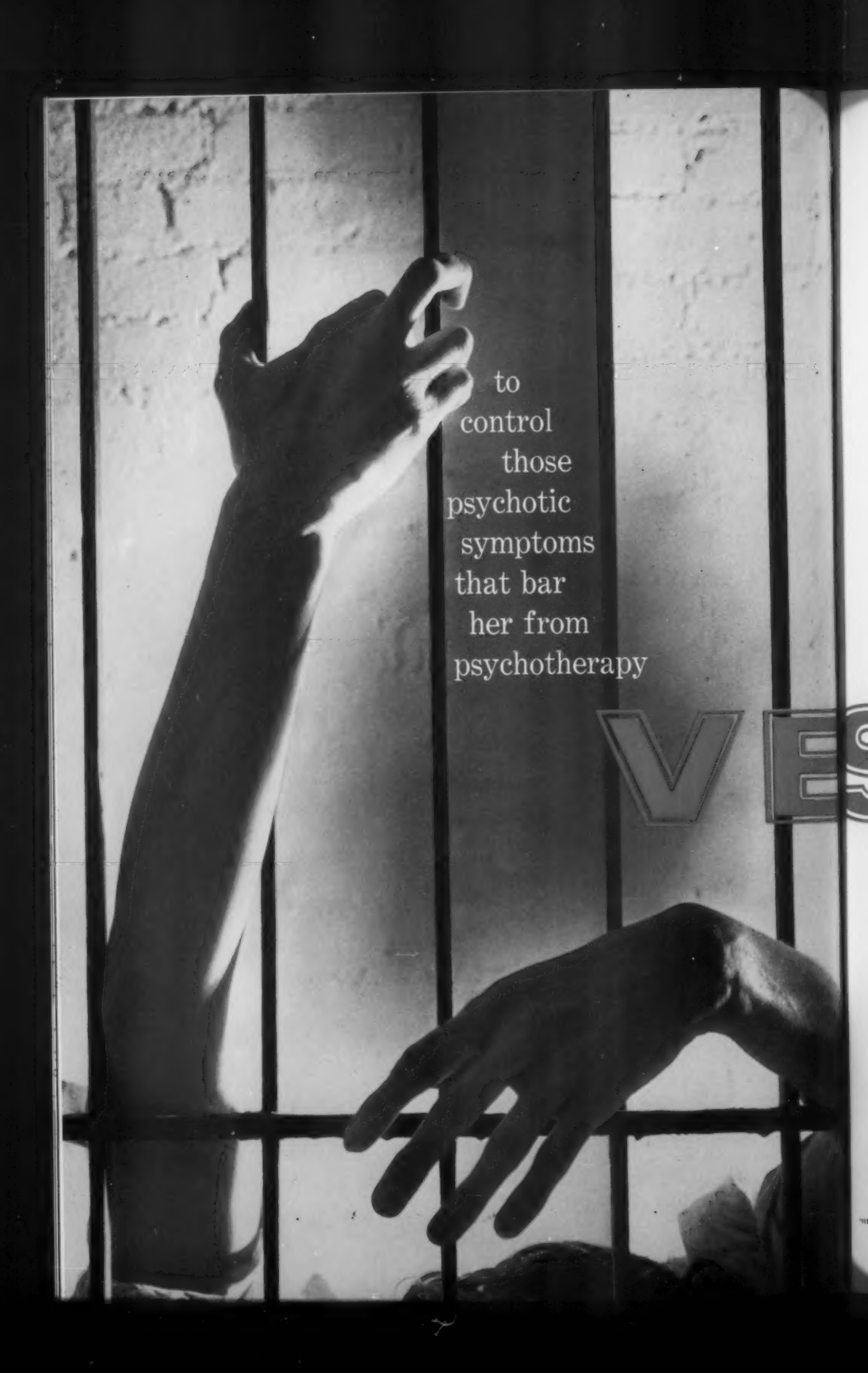
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Neurology Volume 8 • Number 10

Skeletal abnormalities with motor system disease

Leonard T. Kurland, M.D., D.P.H., and
Ntinos C. Myrianthopoulos, Ph.D.

SOME SKELETAL ANOMALIES and sense organ defects occur as distinct genetic entities, for which the mode of inheritance is well known. A few deformities occur so frequently in association with hereditary diseases of the nervous system—for example, pes cavus in Friedreich's ataxia—that they are considered a regular part of the symptom complex or, when occurring alone in ataxic families, a *forme fruste* of the neurologic disorder proper.

A large number of associated physical and neurologic defects of varying complexity do not admit simple genetic explanation because of their irregular occurrence and variable expression. Many of these anomalies occur in one or several members of a family in which a genetically determined neurologic disease has been recognized; however, the combination of anomalies and neurologic diseases is so infrequently described in a consistent pattern that the possibility of a fortuitous association rather than a genetic association cannot be ruled out. On the other hand, the evidence for association of these anomalies to central nervous system disease is too suggestive to be ignored. Examples from the literature will be presented here to illustrate the argument.

In 1889, Gee[1] described a form of hereditary infantile spastic paraplegia in 2 children; their father, who also had symptoms at an early age; and a maternal aunt of the father. Also, 2 of the father's maternal cousins were deaf and dumb and 1 of the individuals was born without fingers.

Fortanier and Speijer[2] described the occurrence of paralysis of the cranial nerves, chiefly facial nerve paresis, in 10 members of a family. Other disorders in the family were idiocy, congenital deafness, dumbness, epicanthus, lacrimal gland anomalies, finger deformities, spina bifida occulta, and external ear malformation. The authors considered paralysis to be transmitted as an irregular dominant but pointed out that one or more of the other abnormalities may have precipitated manifestation of the disease.

Kloos[3] reported a patient who had Huntington's chorea. Her mother apparently had the disease. Her brother and her husband's mother were hard of hearing. Of the patient's 11 children, 3 were deaf-mutes, 2 mentally deficient, and 6 normal. Kloos considered the probability that the defects were primarily due to genetic factors responsible for the chorea. Deaf-mutism associated with retinitis pigmen-

From the Epidemiology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Md.

Read at the tenth annual meeting of the American Academy of Neurology, Philadelphia, April 26, 1958.

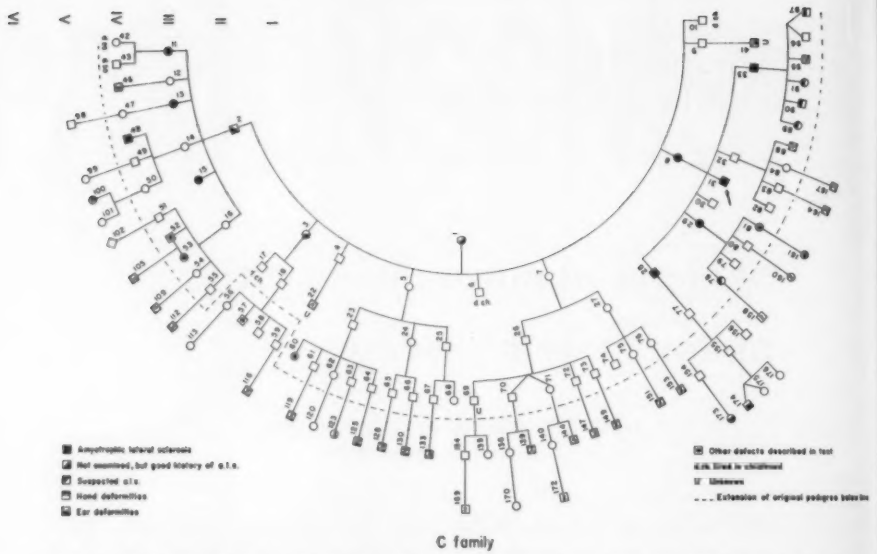

FIG. 1. Pedigree of family C. Individuals below the broken line were traced and investigated since the original pedigree was published.

tosa, mental deficiency, hereditary ataxia, and oligophrenia has been extensively reported in the literature.

Birch-Jensen,[4] in his important 1949 monograph on the congenital deformities of the upper extremities, reported a large and varied collection of central nervous system and developmental defects among the relatives of patients with "endogenous" deformities. These include deaf-mutism, absence of external auditory meatus, congenital blindness, mental deficiency, mental illness, Mongolian idiocy, anencephaly, hydrocephalus, meningocele, spina bifida, clubfoot, deformed feet, paralysis of the lower extremities, harelip, and cleft palate. The author thinks that most of these defects are only chance associations but notes that chance would not provide a good explanation for some, namely, the association of hand defects with congenital blindness, radial defects with lethal conditions, congenital dislocation of the hip with eye and ear defects, syndactyly and symbrachydactyly with thoracic deformities, clubfeet, and mental deficiency. The possibility that some of these defects might be due to prenatal environment rather than a genetic factor cannot be overlooked.

The association of status dysraphicus signs with central nervous system disease has likewise been frequently reported. Finzi[5] found many cases of ear malformations among patients with syringomyelia, and Bremer[6] reported a variety of status dysraphicus signs among relatives of patients with syringomyelia. One of these signs was crumbling of fingers (clinocamptodactyly), which increased toward the ulnar side. Bremer thought that the occurrence of these signs among the relatives could be considered demonstrative of a constitutional factor.

Curtius and Lorenz,[7] after studying a large number of patients with status dysraphicus, concluded that there must be a close relationship between status dysraphicus and certain diseases of the central nervous system, such as hereditary spastic paraplegia, Friedreich's ataxia, and multiple neurofibromatosis.

An excellent review of the problem of status dysraphicus is found in Bijl.[8] Recently, Murakami,[9] who has also reviewed the work on status dysraphicus, reported 2 families with hereditary ataxia; nonaffected members of these families had signs of status dysraphicus, including kyphosis, scoliosis, lordosis, spina

bifida, camptodactyly, clinodactyly, funnel chest, and other stigmata.

It is likely that many cases of the association of anomalies and nervous system diseases are not described in the medical literature. At the risk of presenting a few combinations that might be due to chance, we wish to call attention to our observations so that others in the field may be alerted to the possibility that these anomalies develop in families with motor system disease. A good accumulation of cases, with accurate reporting, will go far in helping to define clinicogenetic entities and to detect possible genetic linkage, about which knowledge is so sadly lacking in man.

PEDIGREES

Family C. The pedigree of family C in Iowa, with 12 cases of amyotrophic lateral sclerosis in four generations, reported by Kurland and Mulder[10] in 1955 has been extended; 2 more generations have been added, making 6 in all. Since several members of the family unknown when the original pedigree was published were traced and interviewed, the numbering of the individual members of the pedigree has been changed (Fig. 1). The propositus is now III-31.

The neurologic and skeletal defects found in several members of this family include: deaf mutism (IV-52), infantile spastic quadriplegia (V-100), ataxic paraplegia and mental deficiency (IV-60), funnel chest deformity (V-81 and VI-161), and—cases we wish to describe in some detail—deformities of the hands (IV-89, 90, 91, and 97) and abnormal development of the ear (VI-173 and 174). None of these defects was found in patients with amyotrophic lateral sclerosis, although III-33 has a mixed deafness that developed in later years.

The deformities of particular attention here have occurred in descendants of II-8. She died at 64 years of age, after an illness of two years' duration characterized by progressive paralysis and muscle wasting, dysarthria, and dysphagia. Amyotrophic lateral sclerosis has been diagnosed in 4 of her 6 children; 3 died after illnesses of about one to three years' duration that developed in the fifth or sixth decade. III-33 developed some muscle atrophy in the lower extremities and some evidence of corticospinal tract changes in 1953, but his illness has been almost stationary in the last three years.

Of the 9 offspring of III-33, bilateral deformity of the hands, which apparently has not been described before, developed in 4 (IV-89, 90, 91, and 97).

The oldest daughter (IV-89), who is now 23 years old, has bilateral, symmetric hand deformity. The defect was present at birth and involves the index and middle fingers (Figs. 2 and 3). In the left hand, the proximal phalanx of the second finger is short and shows ulnar deviation and also subluxation at the joint space. The middle and distal phalanges of the second finger are shorter than normal. The proximal phalanx of the third finger is likewise abnormally formed and shorter and thicker than normal. The deformity of the right hand is similar to that of the left, but the proximal phalanx of the second finger has apparently formed from 2 centers. These centers

FIG. 2. Photographs of the hands of IV-89

FIG. 3. Roentgenogram of the hands of IV-89 showing the deformities of the index and middle fingers.

FIG. 4. Photographs of the hands of IV-97 (*left*) and the normal hands of his fraternal twin, IV-96 (*right*)

FIG. 5. Roentgenograms of the hands of IV-97 and IV-96. The bilateral finger deformity of IV-97 is similar to that of his sister, IV-89, and of the other affected siblings.

have not fused, resulting in a marked ulnar deviation of the second finger.

A brother, age 22 years (IV-90), and a sister, age 20 years (IV-91), have deformities that are almost identical with those of the older sister.

A 5-year-old fraternal twin (IV-97) has a similar bilateral finger deformity, but the hands of the other twin (IV-96) are normal (Figs. 4 and 5). The abnormality involves the proximal phalanges of the index and middle fingers. The accessory ossification centers of these phalanges have not fused. The bone age, based on the development of the carpal bones of the affected twin, is about six months retarded as compared with that of the unaffected twin.

III-28, a brother of III-33, died of amyotrophic lateral sclerosis in 1938. The son of III-28, IV-77, is now 48 years old and apparently well. He has 3 sons, ages 26, 24, and 22 years; all are apparently quite well. Whether any of these individuals will eventually develop amyotrophic lateral sclerosis remains to be seen.

The wives of V-154 and V-155 are not related. V-154 has 1 daughter (VI-173) who was born with an anomaly of the left ear (Fig. 6). V-155 has 3 children, including a set of dizygotic twins. VI-174, one of these twins, was likewise born with an anomaly of the left ear (Fig. 7), while the other siblings appear to be normal. In both of the affected cousins, the auricle is vestigial and there is congenital atresia of the external auditory canal. This appears to be microtia, which usually includes fusion of the malleus and incus and some hypoplasia of the facial nerve.

Roentgenograms of other parts of the skeletal system have disclosed no significant abnormality in these children.

A few children with unilateral microtia have been observed on Guam, where amyotrophic

FIG. 6. Microtia in VI-173, cousin of VI-174

FIG. 7. Microtia in VI-174. His twin sister is normal.

lateral sclerosis is so prevalent (Fig. 8). It is our impression that the incidence of microtia is increased in this population, but, since there are no adequate statistics on the general population, we are unable to make a valid comparison. We have observed no finger deformities on Guam which resemble those described in the family C.

Family S. Amyotrophic lateral sclerosis has been reported[10] in several members of this family from North Dakota (Fig. 9). No extensive investigation of the skeletal abnormalities in this family was made. It was noticed, however, that IV-12, a nephew of the propositus III-5 in the original pedigree, had a right hand skeletal defect. He is a male, 19 years old, second in a sibship of five. The right forearm is fully developed, but the hand is reduced to a stump with 4 rudimentary fingers, bearing fingernails (Fig. 10). A fifth finger, also rudimentary, was present but hung loose and was amputated. The father (III-7 in the original pedigree), age 51 years, is the only sibling in a sibship of 4 who has not been affected with amyotrophic lateral sclerosis.

FIG. 8. Microtia in one of the children observed on the island of Guam

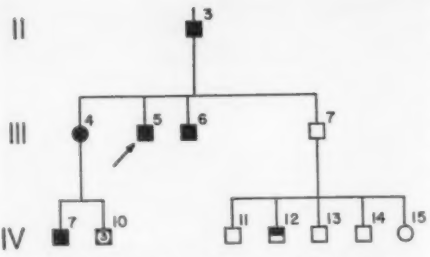

FIG. 9. Part of the pedigree of family S. The complete pedigree can be found in Kurland and Mulder.[10]

DISCUSSION

Since only 1 isolated case of deformity has been described in family S, the discussion will be confined to the deformities found in family C. Actually, these defects are so heterogeneous in nature that a discussion of their occurrence in this family is not expected to resolve the meaning of their apparent or real association with amyotrophic lateral sclerosis. Such discussion is only intended to lead to healthy speculation.

A first question is immediately posed: whether the association of these defects with amyotrophic lateral sclerosis is a purely chance association or whether it is a deeper, genetic-biologic one. Although the chance association cannot be ruled out, it seems an unlikely solution. The occurrence of these defects in a pedigree of 176 persons far exceeds their prevalence in the population, taken either collectively or as individual entities.

Possibly, of course, these defects are genetic entities, assorting independently in this family, which means that the genes for these defects are located on different chromosomes from that of amyotrophic lateral sclerosis or are associated with amyotrophic lateral sclerosis by linkage. The latter possibility is very unlikely because these defects are not found in patients with amyotrophic lateral sclerosis. Independent assortment is a possibility which should be kept in mind, although some of the described defects do not behave according to their known mode of inheritance. For example, the few pedigrees of atresia of the auditory meatus that have been described in the literature are indicative of dominant inheritance. This does not seem to be the case for VI-173 and 174, since their parents and grandparents do not have the defect. To our knowledge, the hand deformity present in IV-89, 90, 91, and 97 has not been previously described, but most of the inherited deformities of the hand known are dominant, which does not seem to be the case here. In contrast, funnel chest, which is inherited as a dominant, behaves as such in IV-81 and her daughter.

FIG. 10. Photograph of the hands of IV-12

Other possibilities should also be considered. As pointed out, the literature contains examples of some skeletal abnormalities that are considered a *forme fruste* of the hereditary neurologic disorder. Whether such a wide variety of skeletal and neurologic defects as observed in family C can be considered *formes frustes* of a central nervous system disease such as amyotrophic lateral sclerosis may be disputed. A better explanation than that of *forme fruste* would be that of variable expressivity of the dominant gene for amyotrophic lateral sclerosis at different ages and in different constitutional types. However, in only 1 instance, that of III-33 and his children, is there any supporting evidence for this possibility. In no other case do the individuals with these defects have a parent affected with amyotrophic lateral sclerosis, although the parents of the children with microtia have not passed through the age at risk for amyotrophic lateral sclerosis. It is possible, of course, that the expressivity of the amyotrophic lateral sclerosis gene in other parents of individuals with various neurologic or skeletal defects was so slight as to escape detection.

The central nervous system diseases that have been reported in association with skeletal anomalies include spastic paraplegia, heredi-

tary ataxias, amyotrophic lateral sclerosis, and others. It is possible that some or all of these diseases are more closely related to one another than is currently assumed, sharing similar neurochemical background with a wide range of expression potential. Such background may operate through separate genetic pathways and produce a spectrum of neurologic signs and symptoms. Perhaps, these manifestations can be classified into broad neurologic entities, but considerable overlapping and shifting of one entity into another may occur. For example, pathologic reports of patients with clinical amyotrophic lateral sclerosis occasionally describe some lesions suggestive of hereditary ataxia. Several cases have come to our attention in which anterior horn cell degeneration and lateral column degeneration were present, but there was demyelinization of the posterior columns and the dorsal spinal cerebellar tracts as well. Recently, Dr. W. Harlan[11] brought to our attention a family with cerebellar ataxia and hand deformities that resembled those described in family C.

It is evident that no simple genetic explanation can be offered for the association of these skeletal and neurologic defects with amyotrophic lateral sclerosis and other central nervous system diseases. The fact remains that reports of associations of this nature are found in the neurologic literature and suggest that the association is genetic rather than pure chance.

In summary, a number of skeletal and neurologic abnormalities are described in a family, several members of which have been affected with amyotrophic lateral sclerosis. Particular attention is paid to microtia and bilateral hand deformities involving the middle and index fingers. Other defects also present in this family include deaf-mutism, spastic quadriplegia, ataxic paraplegia with mental deficiency, and funnel chest. Although chance cannot be ruled out, it seems more likely that there is a genetic association of these abnormalities with amyotrophic lateral sclerosis. Several possible explanations for such an association have been considered.

It is hoped that this presentation will stimulate further interest in this field, because only through careful research will we be able to determine whether this recognized but, at present, ill-defined association is truly genetic.

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Long-range effects of electropallidoansotomy in extrapyramidal and convulsive disorders

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AMONG THE APPLICATIONS of stereotaxic operations (stereoencephalotomy[1]) in man is the production of pallidal lesions in the treatment of involuntary movements, proposed as early as 1947.[2] We performed the first stereotaxic pallidotomy on record in 1948 in a patient with Huntington's chorea. This was reported before the Philadelphia Neurological Society in 1949.[3]

The possible value of such procedures can be evaluated only by long-range follow-up studies. This article will present studies of cases in which electropallidoansotomy – production of lesions of the pallidum and ansa lentiformis by fractionated electrocoagulation– has been performed in 4 groups of disorders: [1] paralysis agitans and parkinsonism,[4,5] [2] other involuntary movements of extrapyramidal origin, [3] certain types of spasticity, and [4] some types of convulsive disorders with subcortical involvement.

PARALYSIS AGITANS AND PARKINSONISM

In the 50 cases of postencephalitic parkinsonism or paralysis agitans making up this group, 71 operations were performed. The postoperative observation period lasted one to six years. In 9 patients, bilateral pallidoansotomy was carried out, with a usual interval of several months between the left- and the right-sided procedures. The age of the patients ranged between 19 and 79 years; the duration of the disease between three and thirty-four years. We found it imperative to perform the operation under local anesthesia whenever possible so that the position of the electrode could be controlled by stimulation prior to the production of the lesion and the effect of each partial lesion on tremor and voluntary movements could be observed.

Of 49 cases with tremor unresponsive to medication, 22 (44.9%) showed a marked reduction or abolition of tremor and 16 (32.6%) showed a moderate tremor reduction, for a total improvement of 77.5%. Duration of the disease had no definite influence upon the results. The patient's age, however, was of importance in that excellent results were obtained in half of patients below 50 and between 50 and 60 years of age and in only about one-fourth of patients over 60 years of age (Table 1).

Rigidity was definitely reduced in 26 (72.2%) of 36 patients so affected prior to surgery. No significant influence of age or duration of the disease in this respect could be found. Recurrence of tremor a few days to twenty months postoperatively was noted in 6 cases; these were patients in whom the lesions had been placed chiefly in anterior parts of the pallidum at the level of the anterior commissure and 3 mm. behind it. In 5 of these cases, the lesion was enlarged at more posterior levels – 6 mm. or 9 mm., if necessary, behind the anterior commissure. This abolished the tremor in 4 patients and reduced it in 1. Improvement has lasted for the observation period of 1 to 5 years.

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TABLE 1
EFFECT OF PALLIDOANSOTOMY ON TREMOR IN VARIOUS AGE GROUPS

Age	*< 40*	*40–50*	*50–60*	*60–70*	*> 70*
Total	*7*	*15*	*16*	*8*	*3*
Excellent*	1	10	9	3	
Improved	4	2	6	2	1
No change	2	3	1	3	2

*Abolition or marked reduction of the tremor.

TABLE 2
AGE DISTRIBUTION OF PATIENTS AND OF COMPLICATIONS

Age	*50*	*50–60*	*60*
Total population	46%	32%	22%
Transient and permanent complications	4%	12%	12%

TABLE 3
REHABILITATION

		Preoperative incapacity	
		Total	*Partial*
Complete			
Engineer	1	1	
Auto mechanic	1	1	
Laborers	3	1	2
Messenger boy	1		1
Housewives	3	1	2
	9	4	5
Partial			
No nursing problem, dress and feed themselves	8	2	6
Changed to lighter work	5	1	4
Physically rehabilitated, not working for other reasons	2		2
	15	3	12

There were 2 deaths in this series, making a case mortality of 4%, and an operative mortality of 2.8%. One patient was a deaf-mute with whom we could not communicate during the operation. The lesion apparently encroached upon the internal capsule so that a hemiplegia ensued, and the patient died four months after operation. The second patient died of congestive heart failure and bronchopneumonia after the second operation. Permanent hemiplegia occurred in 2 patients (4%); transient hemiplegia, lasting a few weeks to several months, in 6 patients (12%); transient facial weakness of one week to ten days' duration in 4 patients (8%); and a transient monoplegia in 2 instances, lasting two to five weeks. Age of the patient seems to influence the appearance of these complications; 46% of patients were in the age group below 50 years: cases with transitory or permanent complications in this age group represented only 4% of all patients. Of all the patients, 32% were between 50 and 60 years of age; the percentage of the complications rising to 12% of all patients. Still more unfavorable is the relationship of age to complications in patients over 60 years of age; although this group represented only 22% of all patients, we found that complications occurred in 12% of all the patients (Table 2).

From a practical point of view, we are, of course, less interested in the effect of the operation upon single symptoms than in the total effect upon the activities or the working capacity of the patient. A complete rehabilitation, enabling the patients to resume their former occupations, was obtained in 9 of 50 patients (18%); partial rehabilitation resulted in 15 (30%). Therefore, a certain degree of rehabilitation was achieved in slightly below half of the patients (Table 3).

The influence of preoperative incapacity upon rehabilitation is shown in Table 4. It was demonstrated that rehabilitation could be achieved in slightly more than one-fourth of the totally incapacitated and in two-thirds of the partially incapacitated patients.

The influence of age is important not only in regard to the appearance of complications, but also in regard to the possibility of rehabilitation in that the ratio of rehabilitated to operated patients decreases with increasing age—reaching zero in patients over 70 years of age (Table 5). The duration of the incapacity does not seem to have a significant effect upon the rehabilitation.

TABLE 4
INFLUENCE OF PREOPERATIVE INCAPACITY UPON REHABILITATION

Total incapacity		*Partial incapacity*		*Died*
22		*27*		*1 after first operation*
				1 after second operation
Complete rehabilitation	*Partial rehabilitation*	*Complete rehabilitation*	*Partial rehabilitation*	
3 (13.2%)	3 (13.2%)	6 (22.2%)	12 (44.4%)	
26.4%		66.6%		

TABLE 5
EFFECT OF AGE ON REHABILITATION

Age		*< 40*	*40–50*	*50–60*	*60–70*	*> 70*
Total		*7*	*15*	*16*	*8*	*3*
Complete rehabilitation	9	1	6	2	0	0
Partial rehabilitation	15	5	3	5	2	0
Complete and partial rehabilitation		6	9	7	2	0
			57.8%		25%	0

OTHER DISORDERS OF EXTRAPYRAMIDAL ORIGIN

In the group of choreas, there were 4 cases of Huntington's chorea.[6–9] In 1 patient, involuntary movements were controlled except for a slight jerking of the shoulder, extensor-flexor movements of the thumb, and extensor movements of the toes on the right side. This improvement has lasted for an observation period of almost nine years. In 2 other patients, a reduction of the movements of the extremities was obtained; it was not possible, however, to influence the involuntary movements of the head in one of these patients – the first patient on whom pallidotomy was performed almost ten years ago. One case of electric chorea and 1 of senile chorea with dystonic features remained uninfluenced.

In a 74-year-old patient with hemiballismus, involuntary movements were controlled by a lesion of the substantia nigra; however, this patient died of bronchopneumonia five weeks after the operation.

Regarding athetosis, one has to bear in mind that this is not a uniform group. We know from the studies of the Vogts,[10] Jacob,[11] and van Bogaert[12] that in some cases histopathologic changes in the pallidum are pronounced, for instance in status dysmyelinisatus and in progressive pallidal atrophy. We have observed a patient in whom a small operative lesion of the pallidum produced a transitory improvement but in whom an increase of this lesion augmented the involuntary movements, this patient died several weeks later, apparently due to exhaustion. Therefore, in further cases of this group we first studied the effect of transitory depression of pallidal function by means of injection of an aqueous solution of Novocain before producing permanent lesions. In two instances in which this Novocain test was negative, we have discontinued further operative attempts.

Definite reduction of the involuntary movements was obtained in a patient with posthemiplegic athetosis in whom depth electrodes showed absence of electrical discharges in the opposite caudate nucleus. This result was maintained for a period of one year after the operation up to her death that was due to cardiac failure with bronchopneumonia.

In two patients with double athetosis, pallidotomy on the side opposite the more pronounced involuntary movements resulted in a definite improvement. Unilateral pallidal lesions effected only a slight reduction of

athetotic movements in 2 patients with cerebral palsy. However, motility could be improved in one of these patients by reduction of the spasticity on the contralateral side. In such patients, the operation is, of course, only part of the therapy used and an intense postoperative retraining program seems to be very important.

One of 2 patients with torsion dystonia or dystonia musculorum deformans remained slightly improved for 1 year but died before an increase of the lesion could be produced. In the second patient, we succeeded in eliminating the abnormal posture for the duration of the observation period of nearly 2 years.

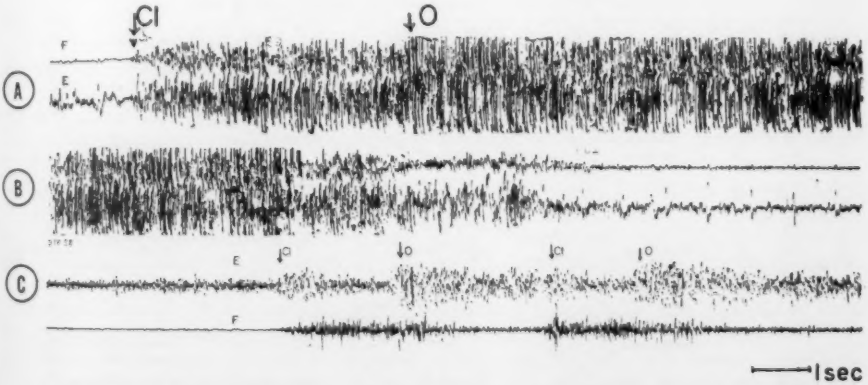
SPASTICITY

It seems of practical as well as of theoretic interest that pallidal lesions are able to diminish the tonus of the skeletal muscles in some cases of spastic paralysis where the existence of increased tendon reflexes and the Babinski phenomenon suggest an involvement of the corticospinal tract. This group was therefore included in our study, although at the present time these cases have been observed only a few months. The participation of extrapyramidal factors in the genesis of at least some types of spasticity is suggested by the observation that sectioning of the pyramidal tract alone[13–17] or of lesions restricted to the cortical area 4[18,19] produces only flaccid paralysis. It has been pointed out previously that, in one of our cases of cerebral palsy, the spasticity was partly reduced on the side opposite the pallidotomy. This was evident in the flexors of the elbow and wrist and to a lesser degree in the flexors of the knee and the adductors of the thigh. Before operation, this patient walked on his toes with the heels elevated from the floor; after the right-sided pallidotomy, the left heel could touch the floor due to reduction of the hypertonicity of the triceps surae muscles.

In a second case of cerebral palsy, there was a flexor contraction of the hand in the wrist and of all fingers of the right side. After pallidotomy, the flexor resistance was definitely diminished in the fingers so that they could be passively extended easily – not possible before operation. In the wrist, the flexor contraction remained.

In two adults with spastic hemiplegia, an influence upon the muscular hypertonicity could not be obtained. However, such an effect was pronounced in the following case. This merits a more detailed description in view of the relief of not only the muscular hypertonicity but also the phenomenon of tonic perseveration of voluntary innervation.[20–22]

This 29-year-old white female had a ruptured ectopic pregnancy in 1950. Several hours later, she experienced a cramp-like sensation of the right side and a numbness and paralysis of the entire left side. The paralysis of the left lower extremity receded so that at the time of discharge she



Spastic hemiplegia with tonic perseveration of voluntary movements. Electromyogram of the flexor (F) and extensor (E) muscles of the left forearm on closing (Cl) and opening (O) of the left hand. *A* and *B* show continuous record before operation; *C* shows record four months after right-sided pallidoansotomy.

could walk, but she had a limp and a deformity of the foot. She gradually recovered some function of the left upper extremity, but there remained a flexor spasticity of the elbow and hand, the latter being clenched in a fist. She had great difficulty in opening this hand; if she grasped an object, she found it impossible to let go, and only prolonged effort permitted her to open the hand gradually by extending one finger at a time. Once the fingers were extended, she was unable to relax the extensor muscles. This tonic perseveration could also be demonstrated by recording the electromyograms of the flexor and extensor muscles of the left forearm (see illustration, A and B). Extensor tone could be suddenly reduced by pressure on the dorsum of the wrist, and, occasionally, voluntary opening of the mouth reduced the flexor spasm of the left hand. She had a residual left central facial weakness and impaired hearing on the left side. There was a marked spasticity of the left upper and lower extremities with hyperactive deep tendon reflexes, positive Hoffman and Babinski responses, and ankle clonus. The great toe had a tendency to remain in dorsiflexion. An equinovarus deformity of the left foot caused her to limp badly. There was marked impairment to pain, touch, and temperature sensations on the entire left side, extending to the midline. Vibration sensation was also impaired on the left side. Coldness of the left hand was complained of subjectively and could be demonstrated objectively. For the past eight years, she has been treated for hyperthyroidism. The diagnosis was a residual spastic hemiplegia following a cerebral vascular accident, most likely an embolism of the middle cerebral artery with tonic perseveration[20–22] on the left hand.

Right-sided pallidotomy was performed on December 16, 1957, at the level of the anterior commissure and 3 mm. behind it. Immediately following production of the lesions, there was a marked reduction of the spasticity on the left side. On the following day, the grip in the left hand was good and the patient could immediately relax her grasp on command. Passive resistance of the muscles to extension or flexion of the wrist and of

TABLE 6

EFFECT OF PALLIDOTOMY UPON CONVULSIVE DISORDERS

Case	*Age*	*Sex*	*Seizures*				*Postoperative observation*	*Remarks*
			Major	*Minor*	*Salaam*	*Other*		
1	10 yr.	M	Abolished	—	Abolished	—	> 3 yr.	Tuberous sclerosis Lesion in area of calcified nodule in caudate nucleus and in pallidum
2	9 yr.	M	Diminished	—	Abolished	—	2 yr.	Subdural hygroma Residual hemiparesis
3*	33 yr.	M	Abolished	Diminished	—	—	> 2½ yr.	Transitory left hemiparesis, reduced initiative
4	6 yr.	M	—	—	Returned	—	> 1 yr.	Tuberous sclerosis
5†	24 yr.	M	Uninfluenced	Uninfluenced	—	—	2½ yr.	Left frontotemporal abscess

*All pallidotomies unilateral except case 3 (bilateral).
†In case 5, a temporal lobe focus is still present and additional amygdalotomy is being considered.

TABLE 7

EFFECT OF PALLIDOAMYGDALOTOMY UPON CONVULSIVE DISORDERS

Case	*Age*	*Sex*	*Seizures*				*Postoperative observation*	*Remarks*
			Major	*Minor*	*Salaam*	*Other*		
6	6 yr.	F	Diminished	Staring spells returned	Abolished	—	1⅓ yr.	Mild right hemiparesis
7	4 yr.	M	—	—	Returned (Miltown controlled)	—	1½ yr.	Postvaccination encephalitis Mental retardation
8	5 yr.	F	Diminished	—	Diminished	—	—	Postvaccination encephalitis Mental retardation
9*	26 yr.	M	Returned	—	—	Psychomotor returned	> 1⅓ yr.	—
10		F	Diminished	—	—	—	1 yr.	Cerebral palsy (scar, left hemisphere)
11	4 yr.	F	—	—	Abolished	—	1 yr.	Mental retardation
12	4 yr.	M	Abolished	—	Abolished	—	½ yr.	—

*Pallidoamygdalotomy in all cases unilateral except case 9 (bilateral pallidotomy and right-sided amygdala lesion).

all fingers was markedly reduced and not significantly greater than that on the normal side. There was still some tendency to hyperextension of the second, third, and fourth fingers on volitional opening of the hand. The left hand now felt warm; whereas, prior to surgery, it had felt cold. On the second postoperative day, she was out of bed and there was a pronounced improvement in her gait. The limp was markedly reduced, and the equinovarus deformity was decidedly diminished. The Babinski phenomenon was still present, but the great toe did not remain in dorsiflexion. The patient was discharged on December 20, 1957.

When examined five weeks and again four months after discharge, she could walk quickly, without limping. Voluntary opening of the left hand and extension of the fingers were only slightly delayed as compared to the right side. Only the left thumb could not be completely extended, and there was hyperextension, particularly of the fourth and fifth fingers. Alternate flexion and extension of the hand could be performed as demonstrated by electromyograms (see illustration, C). Resistance to passive movements of the left hand, arm, foot, and leg was decreased as compared to her preoperative condition. The left hand continued to be warm; before operation, it always felt cold. She could do her housework, peel potatoes, and tie her shoe laces, which she had been unable to do for eight years. The husband noted that while asleep his wife's hand remained in a relaxed, open position. Prior to surgery, the hand was clenched in a fist.

The phenomenon of tonic perseveration,[20,21] also called tonic innervation,[22] has been found in lesions of the frontal lobe, associated with, or independent of, apraxia. In all 3 cases reported,[22] there was evidence of involvement of the corticospinal tract, associated with slight spasticity.

The effect of pallidotomy upon spastic phenomena can perhaps be explained by assuming that the reduction of pallidofugal, facilitating impulses diminishes the discharges from lower subcortical mechanisms upon which the maintenance of static innervation depends and which are in a state of hyperactivity following cortical or capsular lesions. The assumption of facilitating pallidofugal impulses to lower segments is supported on the one hand by the clinical experience that pallidoansotomy is able to reduce states of rigidity in man and on the other hand by animal experiments in which [1] the tremor response induced by stimulation of the mesencephalic tegmentum was augmented by pallidal stimulation or [2] the addition of such a stimulation to subthreshold mesencephalic stimulation was able to elicit a tremor.[23]

CONVULSIVE DISORDERS

It has been pointed out previously that, in some instances, the forebrain ganglia play an important role in the propagation of corticofugal epileptogenous impulses and/or as foci of origin of epileptogenous impulses.[24] The pallidum and amygdala represent nodal points where corticofugal impulses may be interrupted; therefore, we have studied the effect of pallidoansotomy alone or combined with amygdalotomy in a group of epileptic patients in whom seizure discharges were demonstrable in these ganglia and in whom anticonvulsive medication was ineffective. For an evaluation of possible therapeutic effects of such procedures in patients with convulsive disorders, long-range observations are particularly important because improvement of short duration may be considered as a nonspecific effect of the operation. Tables 6 and 7 summarize our observations in 12 cases – 5 pallidotomies and 7 pallidoamygdalotomies. The duration of the postoperative observation ranged in 11 cases from one to over three years. The last case was observed for only six months.

Considering all types of seizures, we were able to control them or markedly diminish their frequency in 7 of the 12 cases (58.3%) despite a drastic reduction of the medication. In 5 patients, the seizures remained uninfluenced or returned partially; for instance, in case 6, only the staring spells returned. In considering these figures, one has to bear in mind that in 4 of the 5 pallidotomies and in 6 of the 7 pallidoamygdalotomies the operation was performed on one side only – the side being determined by the severity of the pathologic changes detected in the depth electrograms of the basal ganglia. It seems of special interest that the so-called salaam convulsions could be favorably influenced; they have been described in the literature under various names: akinetic seizures, static seizures, drop seizures, nodding spasms, or propulsive petit mal. Of 8 cases with salaam seizures, 5 were completely controlled (62.5%), and in 1 instance, these seizures were definitely reduced in frequency (12.5%) – improvement was obtained in three-fourths of the cases. The seizures returned in

2 patients (25%) but became controllable by Miltown in one of them. These observations seem to indicate that in the mechanisms of this type of minor seizures, the basal ganglia play an important part.

SUMMARY

Follow-up studies of stereotaxic operations on the basal ganglia performed from 1948 to 1958 are presented. Fractionated electropallidoansotomy was applied in [1] paralysis agitans and parkinsonism, [2] other involuntary movements of extrapyramidal origin, and [3] certain types of spasticity, including a case of tonic perseveration of voluntary innervation. In a fourth group – convulsive disorders refractory to anticonvulsive medication and showing seizure discharges in the forebrain ganglia – pallidoansotomy was used alone or combined with amygdalotomy.

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Electrooculographic investigation of the caloric response

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In spite of intensive study, the normal parameters of the caloric response have not yet been clearly delineated and there is little general agreement as to what constitutes an abnormal caloric test. A profusion of differing technics for performing the test and a widely varied emphasis on different aspects of the caloric response have further obscured the problem.

The present investigation was carried out in order to [1] study the recording characteristics of the caloric response in the normal subject under various conditions and [2] make an objective comparison of the normal response with the patterns observed in patients with intracranial disease of various types.

The 3 fundamental aspects of the caloric response may be summarized as follows:

- *Nystagmus* with a quick and slow component appears after the introduction of a thermic stimulus into the external auditory canal. If the stimulus is cold, the quick component will be in a direction opposite to the side of stimulation; if warm, the quick component will be toward the stimulated side. Typically, the quality of the nystagmus varies with changes in head position.
- Some manifestation of *postural deviation*, in association with the nystagmus, is usually present in the normal subject. Past pointing, inclination of the head or body, and falling toward the side of stimulation (with cold calorics) or away from the side of stimulation (with warm calorics) are the usual examples.
- *Systemic response*, with vertigo, nausea, vomiting, and diaphoresis often occurs. Oscillopsia may be reported by the subject.

At the present time, electrooculography offers the best means available for objectively studying the ocular reaction to caloric stimulation. With this method, many of the factors that influence the oculomotor response may be analyzed. The effects of eye closure, darkness, fixation, gaze position, and head position are easily ascertained. Analysis of the duration, direction, frequency, and relative amplitude of the nystagmus is facilitated. In addition, the ease of recording and the attainment of an objective and permanent record for purposes of comparison are distinct advantages.

Review of Literature

Many features of the caloric response have been studied objectively, and different criteria have been stressed in an attempt to define the normal physiologic limits of the test. The elements that have been variously quantitated include: the volume and temperature of the stimulus,[1–3] latency time,[4] duration of response and its corollary "directional preponderance,"[5,5–11] frequency and amplitude of the nystagmus,[7,9,11,12] total number of nystagmus beats,[9] total amplitude,[9] eye speed during the slow phase,[10,13,14] intensity of the rapid phase,[9] response decline,[9] amplitude and frequency stability,[11] and "energy of nystagmus."[15] The effect of bilateral simultaneous calorization of the ears has also been studied.[16–18] Other qualities of the nystagmus – its direction, rhythm, and synchrony – have received little attention, and many other variables, such as the effects of eye closure, illumination, and drugs, have not been completely studied.

Observation of the ocular response to caloric stimulation with the unaided eye often results in conflicting reports by different examiners.

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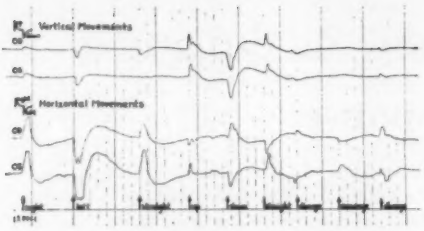

FIG. 1. Normal electrooculographic recording of conjugate eye movements. Veritcal eye movements are indicated by an upward deflection for upward and a downward deflection for downward eye movements.

In the recording of horizontal movements, movements to the right result in an upward and movements to the left a downward deflection of the pens. Polarity of the pen deflection is relative to the preexisting position of the eyes. Thus, a movement of the eyes from a position of left lateral gaze to a position of direct forward gaze will result in an upward deflection of the pens in the horizontal channels.

Head back: horizontal nystagmus

Head erect: horizontal or rotary nystagmus

Head forward: horizontal nystagmus; direction is reversed.

FIG. 2. Basic head positions used during caloric examination. In the head erect position, the head is actually inclined slightly forward from the vertical plane.

This is even more apt to occur when the response is complexly altered or perverted as in some types of intracranial disease.

Electrical recordings of the eye movements by various means have previously been studied in relation to the caloric test.[6,7,9–12,19–25] Most investigators have stressed the amplitude, frequency, and duration of the nystagmus or some variation or derivative of these 3 elements.

METHOD AND MATERIAL

The normal subjects consisted of 16 individuals in whom no evidence of intracranial or external ear disease was apparent. The second group consisted of 49 patients with clinical, roentgenologic, or operative evidence of intracranial disease.

Eye movement recordings were made using the method described by Bergman, Nathanson, and Bender.[26] Standard silver disk electrodes are placed on the skin at the lateral, superior, and inferior orbital margins of each eye and on the bridge of the nose. Leads from these points are then connected with the input of a conventional electroencephalograph. The polarities of the input are adjusted so that, in recordings of vertical movement, an upward deflection for upward movement and a downward deflection for downward movement result; in the horizontal recordings, a right lateral ocular movement deflects upward and a left lateral ocular movement downward (Fig. 1). This permits a direct registration of the direction of eye movement, its frequency, and, to some extent, its amplitude.

Caloric tests in normal subjects were performed with the subject sitting. Observations were then made with the head in 3 basic positions: head back, head erect, and head forward (Fig. 2). Stimulus was provided by 100 to 200 cc. of water at 3 different temperatures—40° C. (warm), 30° C. (cold), and 0-3° C. (ice water). After preliminary otoscopic inspection of the ear canals and tympanic membranes, the water was introduced into the external auditory canal by a syringe attached to a soft rubber tube. At least ten minutes elapsed between initial and subsequent tests on the same or opposite side of each subject. Conditions under which the caloric tests were performed were varied so that the effects of fixation; total darkness; eye closure; gaze position; head position; temperature of the stimulus; drugs (amobarbital sodium) and extraneous visual stimuli (optokinetic and intermittent photic stimulation) could be compared. Recordings were analyzed to determine the direction, frequency, and amplitude characteristics of these variables. Attempts also were made to analyze latency and duration times. At the same time, recordings were obtained from patients with intracranial disease, employing as many of these variables as possible.

RESULTS

Normal subjects

Direction of nystagmus. The most consistent feature of the caloric response in this group was the direction of the nystagmus. During cold calorization, the quick component of the

nystagmus was invariably toward the nonstimulated side, providing the head remained in the head back or head erect position. In the head forward position, reversal occurred and the quick component was directed toward the stimulated side (Fig. 5); during warm calorization, the opposite occurred.

Gaze position. Typically, the cold caloric nystagmus was greatest in amplitude in the abducting eye when the eyes were in lateral gaze away from the side of stimulation (Fig. 3). On direct forward gaze, the amplitude was slightly less, and, when the eyes were directed toward the side of stimulation, the nystagmus was of much smaller amplitude and was occasionally absent. With the reversal of the direction of the nystagmus in the head forward position, the opposite effect was seen, that is, the amplitude was greatest when the eyes were directed toward the side of stimulation and least when the eyes were directed away from the side of stimulation. A parallel change in frequency occurred with changes in gaze position so that a difference of 1 to 2 beats per second was often present between lateral gaze positions, the frequency during contralateral gaze being slightly increased. The warm caloric nystagmus showed a similar, but symmetrically opposite, pattern.

Fixation and darkness. During fixation, with the target approximately 30 cm. from the eyes, and during pursuit movements, fixing at a moving target, caloric nystagmus became smaller in amplitude but increased in rate. If fixation was diminished when the eyes were not fixing at a target and by performing random movements on command, an increase in amplitude occurred while the frequency declined. Fixation was eliminated in total darkness, and further slowing of frequency and increase in amplitude occurred. With the eyes closed lightly, the maximum amplitude and the minimum frequency of the nystagmus were usually achieved (Fig. 4). In the normal subject, for example, the rate was decreased from an average of 4 beats per second during fixation to 1 beat per second when the eyes were closed. In 3 normal subjects, eye closure resulted in immediate inhibition of the caloric nystagmus. That this was not due to a sustained upward movement of the eyes associated with eyelid closure (Bell's phenomenon)

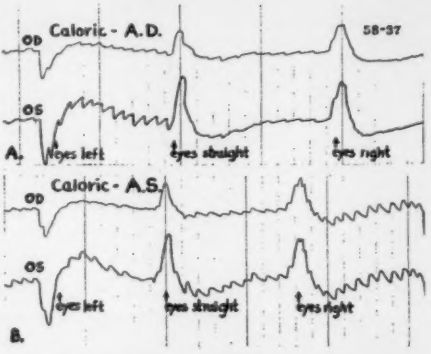

FIG. 3. Effect of gaze position on caloric nystagmus. Horizontal eye movements of normal subject after cold caloric stimulation (0–3° C.) in head back position. *(A)* Right ear: horizontal nystagmus with the quick component to the left. When the eyes were directed to the left, maximum amplitude and frequency resulted. Amplitude and frequency progressively decreased as the eyes moved toward the side of stimulation. *(B)* Left ear: horizontal nystagmus with the quick component to the left. Changes in frequency and amplitude of the nystagmus occurred as the eyes moved toward or away from the side of stimulation.

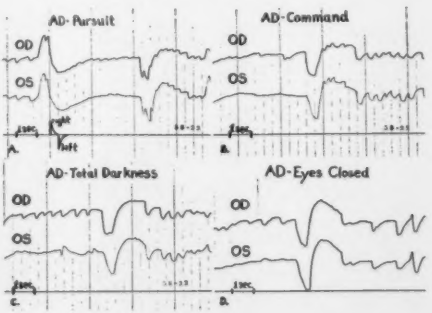

FIG. 4. Effect of fixation, darkness, and eye closure on caloric nystagmus. Horizontal eye movements of normal subject after cold calorization (0–3° C.) of right ear in head back position. *(A)* Fixation on a moving target 30 cm. away. The eyes moved from direct forward gaze to right lateral gaze and then to left lateral gaze. The frequency of the nystagmus was greatest and the amplitude smallest during fixation. *(B)* Random gaze movements performed on command without fixing at a target. The eyes moved from right lateral gaze to left lateral gaze. A slowing of the frequency occurred while the amplitude increased. *(C)* Eye movements performed in total darkness with the eyes open. Further decrease in the frequency with concomitant increase in the amplitude of the nystagmus occurred. *(D)* Eye movements performed with eyes closed. Movement from right gaze to left gaze resulted. The amplitude became maximal, and the frequency was markedly decreased.

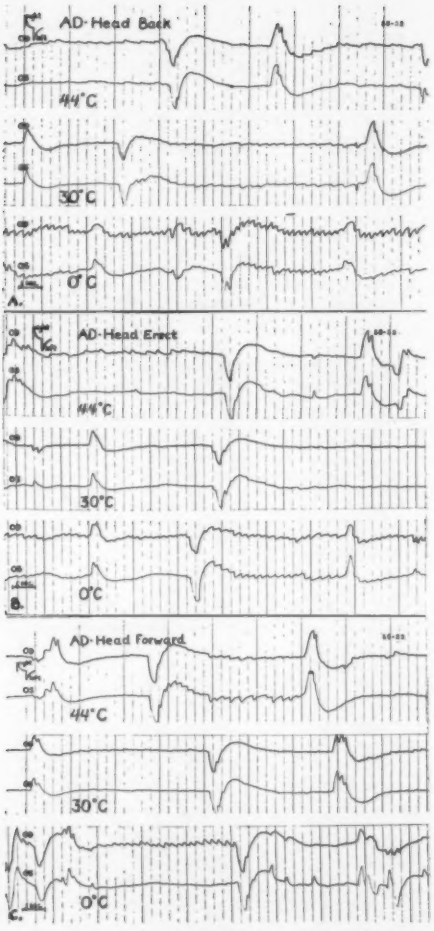

FIG. 5. Effect of stimulus temperature and head position on caloric nystagmus. Horizontal eye movements of normal subject after calorization of right ear at various temperatures in various head positions. *(A)* Head back position: warm calorics (40° C.) resulted in a nystagmus directed toward the side of stimulation. Cold calorics (30° C.) produced nystagmus with quick component away from the side of stimulation. Calorization at 0–3° C. resulted in nystagmus of greater frequency and amplitude than that produced by water at 44 or 30° C. *(B)* Head erect position: direction remained unchanged, but the amplitude of the warm caloric nystagmus increased slightly and the amplitude of the cold caloric nystagmus decreased. *(C)* Head forward position: reversal of the direction of the nystagmus was recorded at each temperature. In the warm caloric test, the nystagmus was directed away from the side of stimulation and, in the cold, the nystagmus was beating toward the side of stimulation. Nystagmus was most apparent when the subject looked away from the side of stimulation on warm calorization and when eyes were directed toward the side of stimulation during cold caloric testing.

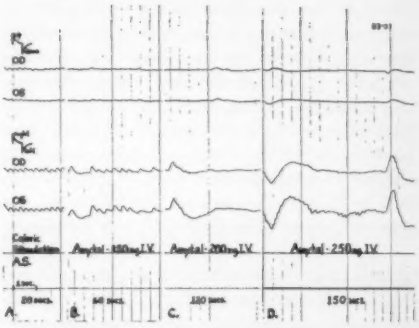

FIG. 6. Effect of barbiturates on caloric nystagmus. Tracings of normal subject following ice water calorics to the left ear in the head back position. *(A)* twenty seconds after appearance of nystagmus before administration of drug. *(B)* Intravenous injection of 150 mg. of Amytal sixty seconds after onset. The nystagmus became less regular, and the frequency decreased. *(C)* The subject had received 200 mg. of Amytal. Caloric nystagmus ceased 120 seconds after onset. *(D)* A high frequency, low amplitude nystagmus of the type typically produced by barbiturates appeared 150 seconds after onset. Subject had received a 250-mg. dose of Amytal.

was suggested by the fact that such subjects were able to perform lateral gaze movements evidenced by their electrical recordings. Occasionally, the nystagmus could be reinstated in such subjects by a sudden loud noise or a noxious stimulus.

Head position. The optimum response, both in frequency and amplitude of the nystagmus, occurred in the head back position. The nystagmus, horizontal in the head back position, was often rotary in quality when the head was erect. The frequency changed only slightly, but the amplitude of the nystagmus was distinctly decreased. When the head was anteflexed forward, the response again became vigorous but the nystagmus reversed in direction (Fig. 5). Except for the direction of the nystagmus, the same effect was observed independent of the stimulus temperature.

Drugs. Most involuntary movements, including spontaneous nystagmus, are altered by barbiturates.[26–28] Amobarbital sodium (Amytal) was injected intravenously during the caloric test, following the appearance of nystagmus. The first effect noted was usually a reduction in the frequency of the nystagmus

and a tendency to less regularity of rhythm (Fig. 6). The frequency further slowed until the caloric nystagmus was completely abolished. Finally, a very fine rapid nystagmus with a quick component corresponding to the direction of gaze became manifest. This nystagmus is characteristic of that induced by barbiturates. These changes in the caloric nystagmus occurred well within the usual duration times of the caloric response in the subjects examined.

Latency time. Great variation in latency, the period of time between the introduction of the stimulus into the external auditory canal and the appearance of nystagmus, was observed. At least ten minutes elapsed between successive tests in a given subject, but the usual observation was that the latency on the side receiving the stimulus last was significantly shorter than the latency of the initially stimulated side. This was observed regardless of the sequence of testing and in the same subject on successive tests; for example, 1 normal subject received 2 successive caloric tests to the right ear followed by 2 to the left ear with the following latencies: right ear—first caloric test, seventy seconds; second caloric test, thirty seconds; left ear—first caloric test, forty-four seconds; second caloric test, twenty seconds. Reversal of the sequence gave similar results.

Temperature. Caloric tests performed at 44 and 30° C. gave comparable results except for the direction of the nystagmus. Not infrequently, however, the resulting nystagmus was present in only one or two positions of gaze. Testing at 0-3° C. invariably resulted in a nystagmus of greater amplitude and somewhat greater frequency, persisting in all positions of gaze (Fig. 5).

Duration. The average duration times of the nystagmus response agreed well with those reported in the literature (120 to 180 seconds) for caloric tests performed at 44 and 30° C. The duration was appreciably increased in caloric tests performed at 0-3° C.; it ranged from 250 to 400 seconds. Contrary to statements in the literature, we have not observed inhibition of the caloric response using a stimulus of this temperature. Serial observations of duration times in the same subject have been incomplete so that no statement concerning the constancy of this aspect of the test can be made.

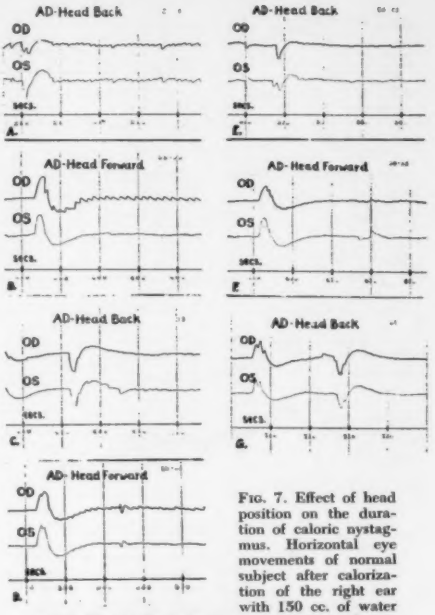

FIG. 7. Effect of head position on the duration of caloric nystagmus. Horizontal eye movements of normal subject after calorization of the right ear with 150 cc. of water at 0-3° C. *(A)* Head back: typical horizontal nystagmus to the left. After 390 seconds, the nystagmus had stopped. *(B)* Head forward: nystagmus immediately reappeared, in reversed direction. As the nystagmus diminished or stopped with time, the head was periodically moved into head back or head forward position. *(C)* Head back: nystagmus reappeared at 443 seconds, but the frequency and amplitude had diminished. *(D)* Head forward: reactivation of nystagmus at 523 seconds with further decline in the amplitude and frequency as compared to *(B)*. *(E)* Head back: persistence of nystagmus at 578 seconds. *(F)* Head forward: after 668 seconds, nystagmus was still present. *(G)* Head back: nystagmus disappeared after 700 seconds.

It was repeatedly observed that the duration of the nystagmus could be considerably prolonged by merely changing the head position; ice water response in the head back position persisted for approximately 390 seconds in 1 normal subject (Fig. 7). The head was then anteflexed forward, and nystagmus immediately reappeared. Subsequently, by periodically changing the head position when the nystagmus declined or disappeared, the response could be reactivated to a final duration time of around 700 seconds. As has been previously observed,[9–11,29] duration was also influenced by other factors such as state of fixation, darkness, and eye closure.

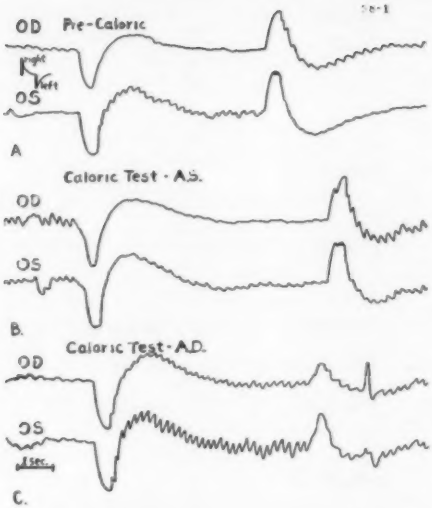

FIG. 8. Elimination of spontaneous nystagmus by caloric stimulation. Horizontal tracing from a patient with lateral gaze nystagmus, tested with ice water calorics in the head back position. *(A)* Nystagmus to the left on left lateral gaze and nystagmus to the right on right lateral gaze. The nystagmus was most apparent in the abducting eye. *(B)* Left ear: the nystagmus on left lateral gaze was converted to a nystagmus with a quick component to the right. *(C)* Right ear: right gaze nystagmus was reversed to a nystagmus with quick component to the left.

Extraneous visual stimuli. Subjects were exposed to simultaneous intermittent photic stimulation at varying frequencies and to optokinetic stimulation with a revolving drum during the caloric response. No consistent effect on the nystagmus was observed with photic stimulation, and during induced optokinetic nystagmus, the caloric nystagmus was usually superimposed on the optokinetic nystagmus.

Patients with Intracranial Disease.

Of the 49 patients with intracranial disease of various causes, 15 patients had cerebral disease; 24 had brain-stem disease, including 6 with cerebellopontile angle tumors; 4 had cerebellar disease; 3 had labyrinthine dysfunction, and 3 had congenital nystagmus.

Abnormal patterns of caloric response not seen in the normal subjects occurred predominantly in patients with brain-stem dysfunction or disease of the posterior fossa. Abnormal response of 4 basic types was seen:

1. *Tonic deviation of the eyes toward the side of stimulation without nystagmus* was a frequently occurring departure from the normal pattern. Responses of this kind are commonly seen in comatose patients irrespective of the etiology, and there is some evidence that responses of this kind correlate with the level of consciousness.[30] This response will also occur in a normal subject if an adequately large dose of intravenous barbiturates is administered.

2. *Tonic deviation of the eyes toward the side of stimulation with persistent contralateral nystagmus* is a second type of abnormal response.

3. *The appearance of a markedly dissociated or perverted nystagmus* can usually be regarded as abnormal, although variations in the nystagmus between the two eyes may occur under certain circumstances in the normal subject, for example, dissociation of amplitude on lateral gaze. Monocular nystagmus may appear, or there may be a dissociation in the direction, frequency, or amplitude of the nystagmus between the two eyes. We have previously reported examples of this type.[31]

4. *The absence of caloric response* is the final abnormal pattern.

Precise measurements of latency and duration times were much less helpful and were sometimes misleading in evaluating caloric responses in patients with intracranial disease.

Detection of the caloric response in the neurologic patient is often difficult since it may be complicated by the presence of an oculomotor abnormality such as a gaze paresis or spontaneous nystagmus. We have recorded and observed that spontaneous nystagmus may be eliminated by the caloric irrigation (Fig. 8); the patient had diffuse disease of the cerebrum and brain stem of undetermined etiology. There was a lateral gaze nystagmus with quick component in the direction of gaze. On stimulation of the left ear with cold water, the nystagmus to the left, previously present on the left lateral gaze, was converted to a nystagmus with a quick component to the right. Similarly, from the right ear, the right lateral gaze nystagmus was converted to a nystagmus to the left.

In some patients, the horizontal nystagmus on lateral gaze may be apparently unaltered

by a caloric stimulation; in such patients, the appearance of nystagmus on direct forward gaze may be a reliable criterion for judging the caloric response, particularly if there is a tendency to reversal with change in head position (Fig. 9).

Patients with nystagmus in all fields of gaze are even more difficult to evaluate. With the aid of electrooculography, however, a definite effect on the frequency of the nystagmus may be apparent from the caloric stimulus. In such instances, there is usually a slowing of the nystagmus when the subject looks toward the side of stimulation; when the gaze is directed away from the side of stimulation, the frequency of the nystagmus is increased (Fig. 10).

The foregoing responses were found to be the most reliable indications of change induced in the spontaneous state by a caloric stimulus in patients with spontaneous nystagmus and other ocular abnormalities. Subsidiary aspects of the caloric test – postural deviations and systemic reactions – were much less reliable.

A unilaterally defective caloric response is easily detected by means of recordings. In the case of a cerebellopontile angle tumor (Fig. 11), the pre- and postcaloric recordings are essentially similar and the spontaneous nystagmus unchanged when the involved side is tested. After caloric stimulation of the opposite, uninvolved side, nystagmus appears on direct forward gaze, nystagmus to the side of stimulation is eliminated, and typical reversal effect is seen in the head forward position.

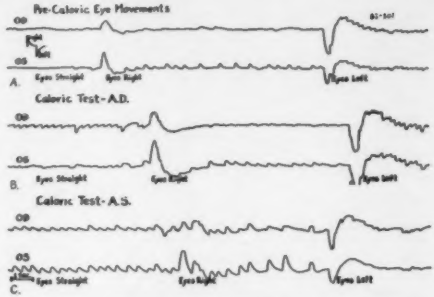

FIG. 9. Appearance of caloric nystagmus on direct forward gaze in the presence of spontaneous nystagmus. Horizontal eye movements of a patient with a partial gaze paresis to the right and lateral gaze nystagmus, tested with ice water calorics in the head back position. *(A)* Dissociated nystagmus on attempted right lateral gaze and binocular horizontal nystagmus to the left on left lateral gaze. Note the absence of nystagmus on direct forward gaze. *(B)* Right ear and *(C)* Left ear: changes induced on the lateral gaze nystagmus were difficult to assess. The most significant change was the appearance of sustained nystagmus on direct forward gaze.

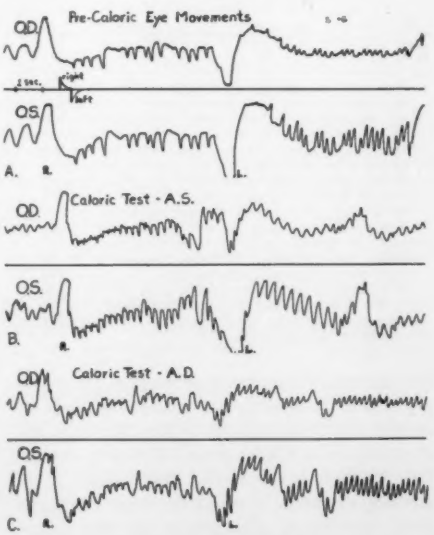

FIG. 10. Effect of caloric stimulation on the frequency of spontaneous nystagmus. Horizontal recordings from a patient with congenital nystagmus tested with ice water calorics in the head back position. Gaze movements to the right are indicated by R., gaze movements to the left by L. *(A)* Precaloric nystagmus. *(B)* Left ear: frequency of nystagmus increased on right lateral gaze, and the nystagmus on left lateral gaze was slowed, becoming sinusoidal in character. *(C)* Right ear: frequency of the nystagmus increased on left lateral gaze.

COMMENT

The ocular phenomena observed after calorization of the ears cannot be regarded as being solely vestibular in origin. In the conscious subject, there are 3 major influences that act upon caloric nystagmus – visual, oculomotor, and vestibular.

Recordings of the effect of vision on caloric nystagmus have been frequently reported.[9,10,23,29,32–34] Fixation causes a detectable increase in the frequency of the nystagmus with a corresponding decrease in amplitude. Nonfixation, total darkness, and eye closure result in a successive decrease in the frequency and an increase in the amplitude of the nystagmus.

If the eyes are closed lightly, nystagmus continues, and the eyes may continue to move in

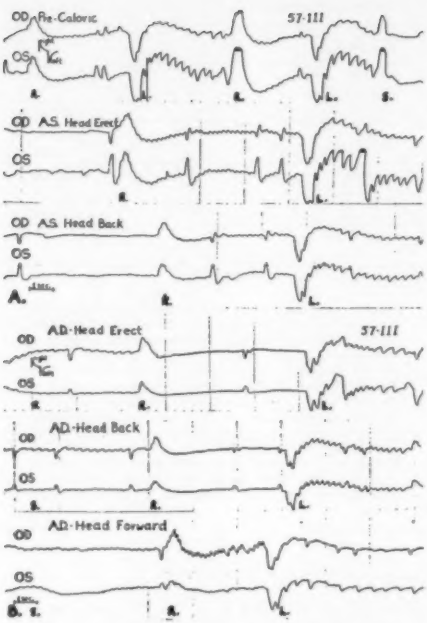

FIG. 11. Unilateral absence of caloric response. Horizontal tracing of a patient with verified acoustic neuroma on the left, tested with ice water calorics. Position of direct forward gaze is indicated by S., right lateral gaze movements by R., and left lateral gaze movements by L. *(A)* Fine nystagmus to the right on right lateral gaze and coarse nystagmus to the left on gaze toward the involved side. Recordings after testing the left ear show little if any significant change in the lateral gaze nystagmus. No change occurred in the head forward position. *(B)* Recordings following calorization of the right ear in 3 head positions show the appearance of nystagmus on direct forward gaze with reversal in the head forward position, and elimination of nystagmus on right lateral gaze in the head back and head erect positions.

the customary horizontal or vertical planes, as evidenced by appropriate changes in polarity on the electrooculogram. When the eyes are forcefully and tightly closed, however, the caloric nystagmus stops, and the subject is apparently unable to perform the usual conjugate gaze movements. The reason for this is not clear, but it is possibly due to Bell's phenomenon. During rapid blinking of the eyes, caloric nystagmus persists but the rhythm is intermittently disrupted by the lid movements. The preexistence of an oculomotor abnormality such as gaze paresis or nystagmus, will also have an altering effect on caloric nystagmus.

Finally, the vestibular system bears the responsibility for initiating the response and is itself subject to many influences, some intrinsic, such as position, and others extrinsic, such as the nature of the stimulus.

Obviously, it is extremely difficult to assess the relative normalcy of the caloric response in any but the simplest and most direct terms. For this reason, we have concentrated on the more qualitative aspects of the ocular response in attempting to separate the abnormal from the normal. Nevertheless, many additional areas of investigation remain to be explored by this method. The study of caloric nystagmus frequencies in various disease states, the effects of different types of drugs, recording of lateralized responses in bilateral simultaneous caloric tests, and the effect of ambient illumination are a few of the obvious possibilities. Electrooculography is an ideal physiologic tool for this purpose. The simplicity of the method and the permanency of the record permit a direct analysis and comparison of each experiment. Once the limits of the normal are established under various conditions of testing, a more accurate determination of the abnormal can be accomplished.

SUMMARY

An electrooculographic study of the caloric response in 16 normal subjects and 49 patients with intracranial disease has been carried out. The following factors were found to influence or modify the caloric test in the normal subject:

- Temperature of the stimulus
- Head position of the subject
- Gaze position of the eyes
- Fixation of the eyes
- Total darkness
- Eye closure
- Amobarbital sodium.

The most constant features were the direction of the nystagmus, change in the quality of the nystagmus with changes in head position, and changes in the frequency of the nystagmus under different conditions. The use of ice water assures a constant temperature of the stimulus and produces a more vigorous and longer lasting response.

Caloric responses in patients with intracranial disease may be modified by:

- Level of consciousness
- Presence of oculomotor abnormality, gaze paresis, nystagmus
- Presence of brain-stem, eighth nerve, or vestibular diseases.

The presence or absence of a caloric response in such patients may be reliably detected by electrooculographic means. Abnormal reactions in this group consisted of [1] tonic deviation without nystagmus, [2] tonic deviation with contralateral nystagmus, [3] dissociated nystagmus, and [4] no response.

The 3 major influences acting upon caloric nystagmus – visual, oculomotor, and vestibular – are discussed.

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Correction

An error appeared on page 534 of the July 1958 issue in the article, "Clinical Evaluation of Spirodon," by Gilbert Frank, M.D., and Frank Morrell, M.D. A square root sign should have been included in the formula for calculating "t."

Impairment of flicker discrimination in brain-damaged patients

Oscar A. Parsons, Ph.D., and Mary M. Huse, M.A.

SOME ENTHUSIASTIC CLAIMS have been made for the effectiveness of flicker-fusion visual field determinations in the identification and localization of brain lesions.[1,2] The evidence presented is not entirely convincing since quantitative support for the conclusions is not given. On the other hand, evidence that flicker-fusion thresholds may provide a more sensitive measure of visual impairment than standard procedures was found by Parsons and Miller.[3] In a study of central flicker-fusion thresholds of patients with multiple sclerosis, it was found that cases with optic atrophy had very low fusion thresholds, indicating a severe impairment of fusion discrimination. Standard visual fields did not reveal scotomata in these patients.

The claims for the relative sensitivity of the flicker-fusion visual field to brain changes might be justified on the basis of the impaired central binocular fusion discrimination accompanying cortical damage which has been reported by many investigators.[1,2,4-7] However, several questions concerning inconsistent findings of threshold values in brain-damaged patients have been raised.[4] These questions involve the problem of location of lesion, e. g., frontal vs. parietal; recency of brain pathology (acute or chronic); and type of patients studied (operated or nonoperated). Further, a recent study by Reitan,[8] using a very clearly identified brain-damaged population, fails to find significant differences in central flicker-fusion thresholds between this group and control subjects.

From consideration of these problems, the specific aims of our research are to [1] develop quantitative measures of impairment of flicker-fusion discrimination in the visual fields, [2] examine the effect of cortical brain damage on visual discrimination as measured by central and perimetric flicker-fusion thresholds, and [3] compare the flicker-fusion fields of patients who have had surgical intervention for brain lesions with patients who have demonstrated cortical damage but have not had surgical intervention.

MATERIAL AND METHOD

Selection of 26 brain-damaged subjects was made from the tumor clinic and from the hospital. Of these patients, 13 had undergone surgical removal of a tumor or brain lesion and 13 had no history of operation but had present unequivocal neurologic signs or neurologic signs and one other positive sign, such as an abnormal electroencephalogram, pneumoencephalogram, or skull film.

The 26 control subjects were matched as closely as possible in terms of age, sex, color, and education. A range of physical disorders was obtained, including some which might have had an effect on brain functioning. However, there were no consistent neurologic findings or other positive signs of brain disturbance in these patients.

In table 1, a comparison of the brain-damaged and control patients on age, education, sex, and color is given. It is evident that the groups are closely equated except for education, brain-damaged patients being significantly higher in educational level; this, however, would serve to reduce differences rather than inflate them. Comparable data for the operated and nonoperated groups of brain-damaged patients are presented in table 2. These sub-

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TABLE 1
COMPARISON OF 26 BRAIN-DAMAGED AND 26 CONTROL SUBJECTS ON AGE, EDUCATION, SEX, AND COLOR

	Brain-damaged				*Control*			
	Age	*Education*	*Sex*	*Color*	*Age*	*Education*	*Sex*	*Color*
Mean	39.6	10.9	M = 18	W = 20	39.2	8.4	M = 18	W = 20
S.D.*	10.2	3.2	F = 8	N = 6	10.9	4.1	F = 8	N = 6

*Standard deviation

TABLE 2
COMPARISON OF 13 OPERATED AND 13 NONOPERATED BRAIN-DAMAGED SUBJECTS ON AGE, EDUCATION, SEX, AND COLOR

	Operated				*Nonoperated*			
	Age	*Education*	*Sex*	*Color*	*Age*	*Education*	*Sex*	*Color*
Mean	37.1	11.3	M = 11	W = 12	42.2	10.6	M = 7	W = 8
S.D.*	9.4	3.6	F = 2	N = 1	10.6	2.8	F = 6	N = 5

*Standard deviation

TABLE 3
COMPARISON OF 26 BRAIN-DAMAGED AND 26 CONTROL SUBJECTS ON FLICKER-FUSION VALUES FOR CENTRAL BINOCULAR AND 10, 20, AND 30° CIRCLES

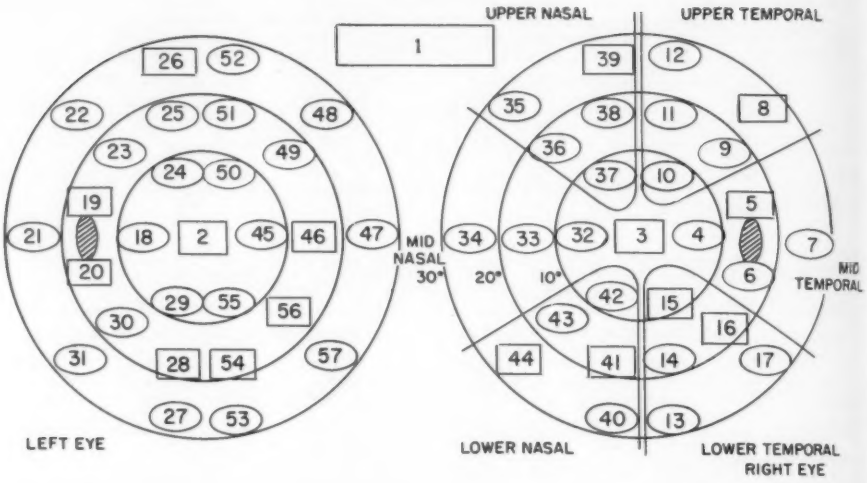
		Central binocular	*10°*	*20°*	*30°*
Control	Mean	40.9	38.1	35.9	33.0
	S.D.*	3.9	5.2	5.1	5.3
Brain-damaged	Mean	36.4	31.2	28.3	25.4
	S.D.	5.0	6.6	6.4	6.4
Difference between	Means	4.5	6.9	7.6	7.6
	"t"	3.60	4.18	4.72	5.89
	P	< .01	< .01	< .01	< .01

*Standard deviation

jects are not as closely matched, except in education. There is little reason to suspect that any of these variables, except age, would affect flicker-fusion thresholds; however, even this variable does not exert a strong effect in the age range studied here. Both brain-damaged and control groups have a −.31 correlation between age and central binocular flicker fusion thresholds.

The apparatus employed was a modification of a standard perimeter. A sliding housing for the light source was mounted in such a way that it could be placed along the arc of the perimeter. The radius of the arc of the perimeter was 410 mm. Directly in front of the chin rest for the subject, a small reddish fixation light was mounted in the center of the arc of the perimeter. The height of the chin rest was such that the eye of the subject and the fixation light were in the same plane.

The target patch was illuminated by a Sylvania glow modulator tube R1131 C. This light source was activated by an electronic unit which provided an input for the tube of essentially square wave form. The size of the target patch was 14 mm., subtending a visual angle of 1.96°. The photometric brightness of the test patch was 5.9 equivalent foot-candles and was dull orange in hue. A light-dark ratio of 50:50 was utilized. The rate of flicker was variable within 8 to 60 cps.



Specific mapping of the visual field, with 28 points plotted for each eye, arranged along 10, 20, and 30° circles. The numbers refer to the order of field plotting, and the squares indicate points at which presentation speed was varied to prevent a temporal set.

The subjects were examined under constant light-adapted conditions. The illumination was provided by a 100-watt incandescent bulb, which was reflected indirectly from the white ceiling of the room, and a recessed bed light. This provided a general level of illumination of .7 ft.-c at the point where the subject viewed the target.

A modification of the method of limits using descending trials only (from fusion to flicker) was employed. After determinations of the central binocular and monocular thresholds, the perimetric examination of fields proceeded.

Each subject was asked to gaze fixedly at the small reddish light directly in front of him and not to shift his gaze from it for the remainder of the examination. The importance of maintaining this fixation was stressed, and the subject was shown how he could see the test patch out of the corner of his eye at the same time. For all thresholds other than the central, the criterion of 2 successive determinations within 3 cycles was followed.

The order of field determination was balanced; one-half of the visual field of the right eye was plotted, followed by the nonhomonymous field of the left eye. The other half fields followed the same order. This was done to prevent possible fatigue of the eye muscles (by alternating the eyes) and central fatigue (by alternating hemispheres). The examination took thirty minutes to an hour to complete.

The specific mapping of the field follows Miles;[1] (see illustration) the numbers inside of the circles and squares refer to the order in which the field was plotted. The squares indicate points at which the speed of presentation was varied in order to prevent a temporal set; 28 points were plotted for each eye. These were arranged along the 10, 20, and 30° circles.

Averages were obtained for each point. Various portions of the visual field were then averaged; for example, the average of points 13, 14, 15, 16, 17 constituted the lower temporal visual field of the right eye.

RESULTS

In considering the results, it is important to emphasize that only those determinations during which the subject could see the light were included; determinations with 0 readings

or scotomata for flicker were not averaged in with other determinations.

At every point and consequently every subportion of the visual field, brain-damaged patients have a significantly lower threshold than the controls, that is, brain-damaged patients manifest a relative impairment in flicker-fusion discrimination. An indication of the magnitude of these differences is given in table 3 where central binocular, 10, 20, and 30° values are given. No differences were obtained at any subportion of the visual field between the operated and the nonoperated brain-damaged groups.

Values for mean absolute discrepancies between nonhomonymous and homonymous fields are presented in table 4. This measure was derived on the basis of the known differential visual field changes accompanying lesions. Comparison of nonhomonymous fields, for example, the temporal and nasal visual fields of the left eye or the temporal fields of the left and right eyes, should give rise to greater discrepancies in threshold than homonymous fields which, except in prechiasmal damage, tend to be more similar. The absolute, rather than the algebraic, sum of discrepancies was utilized because the latter would tend to cancel out if an equal amount of right- and left-sided lesions characterized the group.

The first 4 columns of table 4 are nonhomonymous visual field comparisons. The next 2 columns are homonymous visual field comparisons. Both mean and standard deviations are markedly larger for the brain-damaged group. In view of the heterogeneity of variance, it is questionable whether the reported t tests are appropriate; however, nonparametric tests give rise to the same results – highly significant discrepancies for the brain-damaged patients in the nonhomonymous comparisons. The right temporal versus the left nasal homonymous field also shows a significant difference. This may be due to differential effects of lesion location relative to the optic tract or optic radiation and remains to be investigated more thoroughly.

Comparison of discrepancies between the brain-damaged operated and nonoperated groups again reveals no difference between means; indeed, they are practically identical.

In light of the results presented above, a "visual impairment score" was derived. This consisted of assigning a score of 1 for each of the signs listed at the top of table 5. A central binocular threshold of less than 39 cps received a score of 1; if below 35 cps, an additional score of 1 was given. At the 30° circle, an average threshold of less than 29 cps was scored 1. Discrepancies of 2.5 cps in the 4 nonhomonymous fields were scored 1 each, making a score of 4 for the discrepancy measure possible. The maximal score possible for all signs was 7. The cutoff points for the various signs were derived by taking a combined median score for brain-damaged and control patients on each distribution. The one exception was central binocular vision of less than 35 cps;

TABLE 4

MEAN CYCLES PER SECOND DISCREPANCIES WITHIN EYE AND BETWEEN EYES OF 26 CONTROL AND 26 BRAIN-DAMAGED SUBJECTS

		*Visual field comparisons**					
		Nonhomonymous				*Homonymous*	
		L.T. R.T.	*L.N. R.N.*	*L.T. L.N.*	*R.T. R.N.*	*L.T. R.N.*	*R.T. L.N.*
Control	Mean	1.6	1.2	1.2	1.6	1.4	1.8
	S.D.†	1.5	1.3	1.2	1.2	.3	1.3
Brain-damaged	Mean	5.8	5.1	4.6	4.7	3.3	4.4
	S.D.	5.0	6.4	2.8	4.6	4.9	5.5
Difference between	Means	4.2	3.9	3.4	3.1	1.9	2.6
	"t"	4.0	2.98	5.57	3.29	1.94	2.30
	P	< .01	< .01	< .01	< .01	< .05	< .05

*L = Left, R = Right
T = Temporal, N = Nasal
†Standard deviation

TABLE 5

COMPARISON OF 13 OPERATED AND 13 NONOPERATED BRAIN-DAMAGED AND 26 CONTROL SUBJECTS ON ELEMENTS OF THE "VISUAL IMPAIRMENT" SCORE*

	Central binocular cpc		*30°* cpc	*Discrepancy measure*	*Visual impairment score*
	< 39	< 35	< .29	2 or more†	3 or more‡
Brain-damaged					
Operated	9	5	9	11	10
Nonoperated	9	4	11	12	12
	18	9	20	23	22
Controls	8	1	6	5	4

*Cell entries refer to the number of subjects manifesting signs of visual impairment, for example, 8 control subjects had central binocular thresholds below 39 cps (the median cut-off point) while 18 brain-damaged subjects fell in this category.
†Maximal possible score is 4
‡Maximal possible score is 7

here, the selection was on the basis of a point that was beyond the range of the control subjects.

The entries in table 5 refer to the number of subjects manifesting a given sign. For example, 8 of the control compared with 18 of the brain-damaged subjects have central binocular thresholds below 39 cps. At the 30° circle, 20 of the brain-damaged and 6 of the control subjects have thresholds below 29 cps. The number of subjects having 2 or more discrepancies of 2.5 cps or above is 5 for the control and 23 for the brain-damaged group. Of the individual signs, the "discrepancy" measure gives the best discrimination. The chi-square test for all signs listed in table 5 is significant at the .05 level or better. No differences between the operated and nonoperated patients are found.

The visual impairment score gives the best over-all discrimination. Using a median cut-off point of 3 and above, only 4 of the controls are misidentified (false-positives) while 22 of the 26 brain-damaged subjects are correctly identified. The distribution of visual impairment scores is presented in table 6.

TABLE 6

DISTRIBUTION OF VISUAL IMPAIRMENT SCORES IN THE BRAIN-DAMAGED AND CONTROL GROUPS

	Visual impairment scale	*Number of control subjects*	*Number of brain-damaged subjects*
	7	0	4
	6	0	5
	5	1	5
	4	1	4
Median	3	2	4
	2	7	3
	1	7	1
	0	8	0

DISCUSSION

These results confirm reports in the literature of lowered central flicker-fusion thresholds in brain-damaged individuals.[1,2,4–7] Also confirmed are the results of Battersby[4] and Teuber[7] regarding the gradient of flicker along the horizontal meridian and the relatively greater impairment in the peripheral discrimination of brain-damaged subjects.

Miles'[7] contention that flicker-fusion threshold field examinations provide valuable information regarding visual impairment associated with brain damage is also supported by these findings.

The quantitative possibilities of the flicker-fusion examination are best revealed by the discrimination between brain-damaged and control subjects obtained with the discrepancy measures. The possibility of utilizing this examination for diagnostic purposes is heightened by the fact that the nonoperated and the operated groups showed the same patterns of visual impairment scoring. No significant

difference between these groups was found on any of the visual impairment signs.

While the number of patients is too small to systematically investigate the relationship between locus of lesion and flicker-fusion threshold, it is noteworthy that 3 of the 4 brain-damaged "false negatives," as designated by the visual impairment score, were patients with frontal lobe tumors which had been removed. The other 2 patients with frontal lobe tumors which were correctly identified as having brain damage had, in one case, the optic chiasm exposed during the operation, and, in the other case, 3 operations for a recurrent growth. It would appear that circumscribed frontal damage does not affect flicker-fusion thresholds as Battersby has maintained.[4] However, any damage to postfrontal areas seems to result in visual field impairment. The 4 "false positives" designated by the visual impairment score, included 1 case with a homonymous lowering of flicker thresholds, indicating the possibility of a small brain lesion or, perhaps, in light of the case history, a mild stroke; another appeared to have prechiasmal damage, which resulted in one eye having much lower flicker-fusion threshold values; and the other 2 patients had no obvious reason for their misclassification.

In light of these results, it would appear that the plotting of the flicker-fusion visual field thresholds may be a promising research as well as diagnostic technic.

SUMMARY

The flicker-fusion visual fields of 13 operated and 13 nonoperated brain-damaged patients are compared with those of 26 patients with no evidence of central nervous system disorder. Flicker was produced by an electronically controlled glow modulator tube which was mounted on an adaptation of a standard perimeter, with 28 descending trial threshold determinations being made in each eye, arranged on the 10, 20, and 30° circles.

The following results are obtained:

- The brain-damaged group has significantly lower flicker-fusion thresholds at every point, including central monocular and binocular positions, and significantly larger discrepancies in thresholds in nonhomonymous fields.
- A combined "visual impairment" score correctly identifies 22 of 26 brain-damaged and 22 of 26 control subjects.
- Both operated and nonoperated brain-damaged subjects manifest the same degree of visual impairment.

It is concluded that the plotting of flicker-fusion visual fields is a promising research and diagnostic technic.

Thanks are due to Dr. Louis D. Cohen, departments of Psychology and Psychiatry, Duke University and Duke University Medical Center, for aid in developing the apparatus used in this study. Appreciation is also expressed to Drs. Barnes Woodhall and Guy Odom of the Department of Neurosurgery, Duke University Medical Center, for making available the brain-damaged, operated patients. Dr. Talmadge Peele, departments of Anatomy and Neurology, provided valuable advice in the selection of the remaining patients.

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Multiple sclerosis and allied diseases in Japan

Clinical characteristics

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MULTIPLE SCLEROSIS is said to be more prevalent in the temperate zones of North America, western Europe, and Australia than in the subtropical or tropical zones of these same continents.[1–5] There is still some controversy as to whether susceptibility is related to race and national origin or to an environmental factor that affects all races in the same geographic area equally.

As early as 1911, multiple sclerosis was said to be almost nonexistent in Japan.[6–8] It is the general belief that this disease is also rare among other Oriental populations. In 1929, Woods[9] found only 6 cases among the 4,000 neurologic cases in the Peking Union Medical College. In 1955, Imamura[10] reviewed the Japanese literature and collected 179 cases of multiple sclerosis and its allied diseases. Although beriberi (thiamine deficiency neuritis) has been regarded as one of the important causes of retrobulbar neuritis, Kuwajima[11,12] stressed multiple sclerosis as an important cause of retrobulbar neuritis, a common disease in Japan.

One wonders, in view of the general belief that multiple sclerosis is rare or absent in Japan, whether neurologic practice in Japan is going through the same stages as that in the United States some years ago. Even as late as 1921, multiple sclerosis was considered to be less prevalent in the United States than in Europe. However, the studies of MacLean and Berkson[13] in Rochester, Minn., and the population surveys of Ipsen[14] and Kurland[15] in Boston reveal that multiple sclerosis prevalence is about as high as in equally populated areas in Europe. Whether history will repeat itself in Japan remains to be seen.

In this paper we tried to answer the following questions, utilizing wider sources of information than before:

Does multiple sclerosis exist in Japan?

Do the clinical features of multiple sclerosis and neuromyelitis optica differ from those in the United States or in the European countries?

METHOD OF STUDY

We have collected cases of demyelinating diseases of unknown etiology, such as multiple sclerosis, neuromyelitis optica, and Schilder's disease, from various sources of material in Japan. Parainfectious and postvaccinal encephalomyelitis were excluded. Sources included: [1] previous publications; [2] inquiries sent to all medical schools and major medical centers in Japan; and [3] hospital records in the University of Tokyo over the last several years.

The total number of the cases reported from 1890 to 1955 was 270 (Table 1). Of these, 88 cases were diagnosed during 1953-55. This marked increase in diagnosed cases in recent years may be due to better recognition of the diseases. Another interesting point is that multiple sclerosis is rare when compared to neuromyelitis optica.

The incidence of demyelinating disease among neurologic admissions in the Tokyo University Hospital is 0.9%; multiple sclerosis accounts for only 0.1%; neuromyelitis optica for 0.6%; 0.2% are unclassified. During the past twenty years in the department of pathology, autopsy was done in 7 cases of acute multiple

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TABLE 1
DEMYELINATING DISEASES IN JAPAN*

Types	*1890–1952*	*1953–55*	*Total*
Multiple sclerosis	48	19	66
Neuromyelitis optica	124	51	175
Schilder's disease	2	2	4
Unclassified	8	17	25
Total	182	88	270

*Demyelinating diseases of known etiology (postvaccinal, post- or parainfectious) were excluded.

TABLE 2
INITIAL SYMPTOMS OF MULTIPLE SCLEROSIS (44 CASES)

Symptom	*Cases*
Weakness or disturbance of gait	18
Impaired vision	9
Headache	9
Sensory disturbances	9
Orbital pain	5
Sphincter impairment	4
Speech disturbance	4
Diplopia	4
Dizziness	4
Ataxia	3
Nystagmus	2
Mental changes	2
Disturbance in sweating	2
Stiff shoulders	2
Dullness	2

TABLE 3
SYMPTOMS DURING PROGRESS OF MULTIPLE SCLEROSIS (44 CASES)

Symptom	*Cases*
Ocular manifestations and optic changes	
Nystagmus	25
Weakness of third, fourth, or sixth cranial nerves	19
Paralysis of conjugate gaze	2
Impaired vision	24
Changes of optic disks	23
Defects in visual fields	17
Reflex disturbances	
Deep reflexes of extremities increased	29
Abdominal reflexes diminished or absent	29
Pathologic reflexes present	18
Motor disturbances	
Weakness of one or more extremities	30
Weakness of third, fourth, or sixth cranial nerves	19
Evidence of facial weakness	6
Weakness of other cranial nerves	10
Rigidity	5
Speech disturbances	29
Cerebellar disturbances	
Intention tremor	24
Ataxia	19
Adiadochokinesis	5
Disturbances of urogenital system	22
Sensory disturbances	21
Mental changes	20
Forced laughing	8
Convulsions	6

sclerosis or neuromyelitis optica among 771 neurologic cases.

MULTIPLE SCLEROSIS

Although in Japan there has been no autopsied case, which has been uncontrovertibly proved as typical chronic multiple sclerosis, 66 clinical cases were suspected of being multiple sclerosis. Of these 66, we investigated the records of 44. The age of onset of the illness in the 44 patients is shown in Figure 1. Median age is 31 years, with about two-thirds of patients between 21 and 35 years. Both sexes were equally affected; 23 patients were male, 21 female.

The disease began suddenly in 17 patients, insidiously in 26. In 17 instances, the condition started monosymptomatically, with multiple symptoms in 26. This ratio agrees with that reported by Marquézy.[16]

The initial symptoms are shown in Table 2. Symptoms observed during the course of the illness were nystagmus, optic atrophy, increased deep reflexes, absent abdominal reflexes, positive pyramidal signs, weakness of the extremities, speech defect, intention tremor, and sphincter disturbances; these indicated the multiplicity of lesions in the neuraxis (Table 3). Among 29 patients with speech disturbances, 15 showed scanning and 12 monotonous speech.

NEUROMYELITIS OPTICA

The median age of onset is 25 years, with about two-thirds of patients between 10 and 40 years of age (Fig. 2). About 37% fell ill

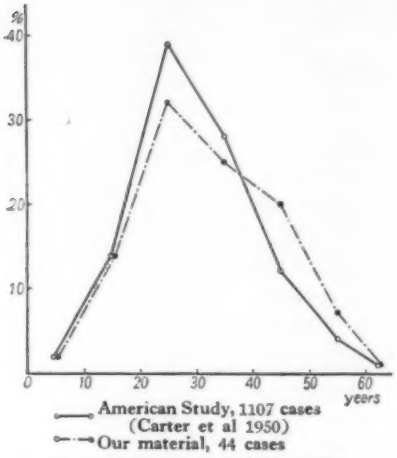

FIG. 1. Age at onset of multiple sclerosis

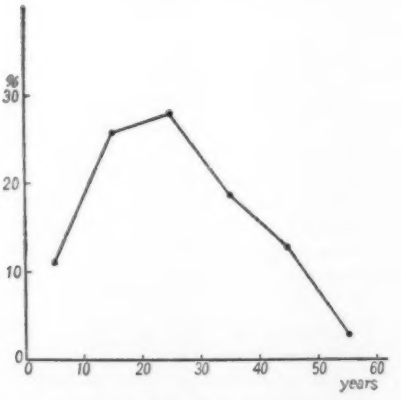

FIG. 2. Age at onset of neuromyelitis optica

before the age of 20. Both sexes were equally affected.

In most cases, the illness began acutely. The initial symptom was loss of vision in 62 patients, spinal involvement in 32, and simultaneous involvement of the two systems in 23.

Loss of vision. In about 87%, loss of vision was bilateral. In most cases, the loss was severe, with blindness in about 60%.

Myelitis. In about half of patients, motor and sensory disturbances were observed in the lower half of the body.

TABLE 4

CEREBRAL SIGNS AND DISTURBANCES OF CRANIAL NERVES IN NEUROMYELITIS OPTICA (30 CASES)

Signs	*Cases*
Speech difficulties	14
Nystagmus	12
Swallowing difficulties	12
Mental changes	8
Disturbance of consciousness	5
External ophthalmoplegia	4
Intention tremor	3
Facial weakness	3
Aphasia	2
Trigeminal nerve impairment	2
Athetosis	1

Other symptoms. Signs of involvement in other parts of the neuraxis were sometimes noted, although they were slight in their manifestations. Cerebral signs and/or disturbance of cranial nerves were observed in 30 patients. Symptoms are indicated in Table 4.

Cerebrospinal fluid. Initial pressure was increased in about one-third of patients in the acute phase but was normal later. Pleocytosis of moderate degree was also often observed during the acute phase. Protein content was normal or slightly increased.

Course. The disease took 1 of 3 courses: [1] regression; [2] remission and exacerbation; or [3] progression or longstanding disturbance (Table 5). In most patients, remission or recovery occurred. Of 104 patients, 29 died during the period of observation, 19 within one year of onset.

Some neurologists consider neuromyelitis optica and multiple sclerosis as different diseases and emphasize the distinction in pathologic findings. Others regard neuromyelitis optica as a variant form of multiple sclerosis. Among the cases of neuromyelitis optica in this material were some that showed marked remittent courses or nystagmus or other cerebral signs. To answer the question of whether or not such cases might be multiple sclerosis, we would like to present two autopsied cases.

Case 1. In March 1949, a 20-year-old woman became blind in both eyes. Within six weeks, her vision returned to normal. Three months after the onset, paresis of the right arm

TABLE 5

COURSE OF NEUROMYELITIS OPTICA

Course		Observed Period: Less than one year	Observed Period: More than one year	Total
Recovered		33	3	36
One or several remissions and exacerbations	Survived	19	13	32
	Dead	10	8	18
Progressive or long-standing course.	Survived	5	2	7
No remission	Dead	9	2	11
Total		79	28	104

occurred with slight fever, which improved within one month. Five months after the onset, flaccid paraplegia and sensory loss up to the nipple occurred suddenly, which almost completely disappeared within two or three days. In November, motor aphasia occurred, lasting several days. In December, transverse myelitis recurred, but she recovered completely from this disturbance within eight months. Toward the end of 1949, visual impairment recurred which showed some fluctuations. She was admitted to our clinic on November 12, 1953.

Neurologic examination at the first admission showed a well developed young woman. Loss of vision was severe, with blindness in the left eye and detection hand movement in the right. Ophthalmoscopic study revealed bilateral atrophy of the optic nerves.

No motor disturbance was noted. Slight hypesthesia was noticed in the distal portions of the right extremities. Hyperactive deep reflexes in the legs, positive pyramidal signs, and absent abdominal reflexes were found bilaterally. Cerebrospinal fluid was normal. Wassermann reactions of serum and cerebrospinal fluid were negative. She was discharged from the hospital two months later.

In March 1954, five years after the onset, severe transverse myelitis recurred and the patient was readmitted to the hospital. Respiration became difficult, and nystagmoid movements were seen transiently. However, these symptoms also gradually diminished. On September 17, she developed frequent tonic convulsions, which lasted several days. In October she again developed convulsions and showed symptoms of meningeal irritation, dyspnea, speech difficulty, and coma. She died in October; the clinical diagnosis was neuromyelitis optica, with marked remissions and slight cerebral involvement.

Macroscopic observations. The optic nerve and spinal cord were atrophic. The brain appeared normal. On section, the spinal cord revealed marked necrotic changes; the brain revealed disseminated lesions in corpus callosum, subcortical white matter, and basal ganglia. Most of the lesions were distinguished as brown flecks, but those in the basal ganglia were necrotic or softened foci. Similar but lesser changes were seen in the pons and medulla oblongata.

Microscopic examinations. The entire optic nerve was demyelinated (Fig. 3). Over the whole length of the spinal cord, irregular and distinct spots of demyelination were found. The demyelinating lesions were chiefly located in the white matter, but the gray matter was also involved. Gliosis was found in the lesion. In the cerebrum were several macroscopic foci which showed demyelination or necrosis (Fig. 4). In the white matter adjacent to the lateral ventricle were demyelinating foci with gliosis.

Comment. This case can be diagnosed pathologically as neuromyelitis optica because [1] lesions of the optic nerve and the spinal cord were predominant; [2] the gray matter was also involved; [3] some of the lesions were necrotic or softened; and [4] cellular reactions were marked. On the other hand, this case

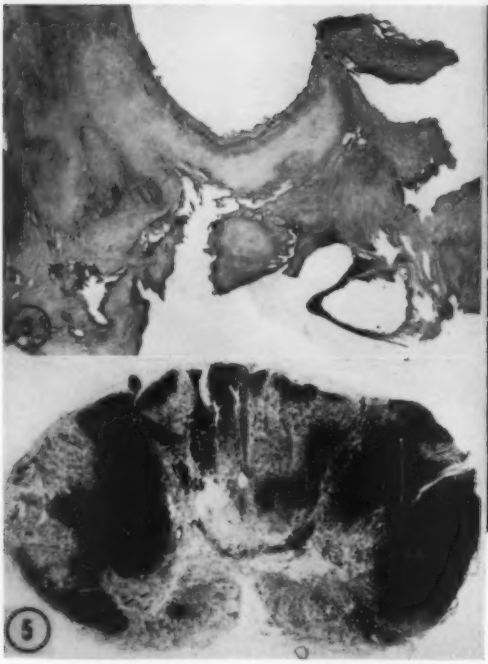

FIG. 3. Section of the optic chiasm, showing complete demyelination (Weigert stain)
FIG. 4. Demyelination and necrosis of basal ganglia and thalamus (Weigert stain)
FIG. 5. Section of thoracic cord, showing extensive demyelination of gray and white matter (Weigert stain). Note softening in the ventral horn.

may not be considered typical neuromyelitis optica but, rather, closely related to multiple sclerosis because: [1] marked remissions and exacerbations were observed several times; [2] slight nystagmus and speech disturbances were present; [3] disseminated lesions were found in the brain; and [4] old disseminated plaques were mixed with new demyelinating foci.

Case 2. In October 1949, a 25-year-old man suffered visual loss followed by disturbance of gait. A few weeks before admission on May 23, 1951, paraplegia of the legs appeared.

The principal neurologic symptoms on admission were as follows: right vision, 0.2; left vision, hand movement. The right disk was slightly hyperemic, and slight pallor was observed in the left disk with conus temporalis. Both legs exhibited flaccid paralysis, and hypesthesia was present below the level of the upper chest. Both arms were ataxic. Superficial abdominal reflexes were very weak. Cerebrospinal fluid was clear and normal in protein content, but cell count was 17 per millimeter.[3] Wassermann reaction of serum and cerebrospinal fluid was negative.

After admission, the symptoms gradually improved. In July, a paresthetic and neuralgic bout occurred in the legs. In August, the patient had tonic cramps. Incomplete paresis of the lower extremities appeared but soon improved. Ten months after admission, paraplegia of the legs reappeared, followed by paralysis of the upper extremities and difficulty in swallowing. One month after this exacerbation, the patient had dyspnea which improved within two weeks. Fourteen months after admission, the visual disturbance increased. Death from sepsis occurred two years after admission, about three years and nine months after onset. The clinical course was characterized by repeated complete remissions.

At autopsy, atrophy of the optic nerve and thinning of the spinal cord, especially at the thoracic level, were marked, but the brain was grossly normal. In the atrophied optic nerve

was a fairly large softened area with vascular proliferation. In the remaining part of the atrophied optic nerve, rarefaction of parenchyma and a slight increase of glial cells were observed.

In the spinal cord, disseminated demyelinated or softened areas were present (Fig. 5). The demyelinated areas were not restricted to the white matter but extended to the gray matter, with involvement of nerve cells and the axis cylinder. In the cerebrum, small demyelinated areas were found only near subependymal parts of the posterior horns of the lateral ventricles and at the upper part of the lateral geniculate body. No change was found in other parts.

In the new demyelinated areas, proliferation of glial cells and perivascular infiltration of the lymphocytes and plasma cells were found. Vascular proliferation was also noted in the foci.

Comment. This case might be diagnosed as neuromyelitis optica according to the clinical findings, although there were marked remissions and exacerbations.

Pathologic findings support neuromyelitis optica because [1] changes of the optic nerve and of the spinal cord were predominant; [2] the gray matter of the spinal cord was also affected; and [3] there were small cavities with vascular proliferation and cellular infiltration. The small demyelinated areas in the brain do not exclude the diagnosis of neuromyelitis optica. Despite marked remissions and symptomatic demyelinating lesions in the brain, the histologic picture was different from that of typical multiple sclerosis and rather close to that of neuromyelitis optica.

DISCUSSION AND CONCLUSIONS

In spite of absence of pathologic verification, it is quite proper to conclude that multiple sclerosis exists in Japan. Age at onset is almost identical with other reports.[5,17] The sex ratio, 1:1, is close to that in the United States and Canada, as are the clinical symptoms. Recently, 2 clinical cases of multiple sclerosis were reported in Japan.[18,19]

The frequency of multiple sclerosis among the neurologic admissions in the University Hospital was 0.1%, which seems to be a smaller percentage than that found in some reports. Jelliffe[20] found that 0.3% of the neurologic and psychologic cases seen at the Vanderbilt Clinic in New York were diagnosed as having multiple sclerosis. Wechsler[21] studied records of 2 New York hospitals from 1912 to 1921 and concluded that 3.4% of the neurologic admissions were due to multiple sclerosis. Brain[22] found that, from 1924 to 1928, 8.1% of the patients seen for "organic diseases of the nervous system" at the Hospital for Epilepsy and Paralysis, Maida Vale, London, had multiple sclerosis. Wilson[23] found that the disease accounted for 6.7% of the organic neurologic admissions to the National Hospital, Queen's Square, London, for the seventeen years before 1925 and that this represented the most important cause of admission, outranking both intracranial tumors and neurosyphilis. Schaltenbrand reported 8% incidence among his neurologic cases in Würzburg. Woods[9] reported that multiple sclerosis had been diagnosed in 6 of 4,000 neurologic patients in the Peking Union Medical College. Rates are difficult to compare because of differences in disease problems and hospital admission practices in these countries, but it seems true that multiple sclerosis is not so prevalent in Japan as in the northern United States and European countries.

The clinical features of neuromyelitis optica are quite similar to those of cases in the Western countries. Besides the cardinal symptoms of the optic nerve and the spinal cord, slight involvements of the brain stem or the cerebrum also occurs. These facts were pointed out by various investigators (Devic,[24] Wilson,[25] Jumentié and Valière-Vialeix,[26] Genet and Devic,[26] Cestàn, Riser and Planques,[26] and Marinesco and associates[26]). Barrera[27] suggested ophthalmo-encephalo-myelopathy as a more appropriate name for the disease.

In many cases, there were marked remissions and exacerbations as in multiple sclerosis. Beck,[28] and Perritt[29] drew attention to the occurrence of remissions in the course of neuromyelitis optica. Perritt found that almost 50% of the recorded cases have been characterized by remissions, a surprisingly high percentage in comparison with the estimates of others (Stansbury[30]). In many cases with remissions, the disease has eventually proved to be multiple sclerosis.

At present, the difference between neuromyelitis optica and multiple sclerosis is not clear. Some features of our cases indicate that there might be transitional or intermediate form between multiple sclerosis and neuromyelitis optica. Stansbury collected 20 autopsied cases of neuromyelitis optica; 5 had lesions in the cerebral hemisphere, 12 in the brain stem, although the pathologic pictures were compatible to neuromyelitis optica. Our cases of neuromyelitis optica were similar to those reviewed by Stansbury.

Prognosis of this disease is said to be very serious. The largest group of patients in literature died in a remarkably short time, with the course progressing to death in the initial attack. In our patients, the prognosis seems to be better than that of those in the West, but, of course, the survival period might be much less than that of multiple sclerosis in the United States and Canada. Kurland indicates average life expectancy of multiple sclerosis is twenty-one years.

In the Western countries, neuromyelitis optica is considered rarer than multiple sclerosis. Among 46 cases of multiple sclerosis, the spinal optic type was seen in only 4. In our material, there were more cases of neuromyelitis optica than multiple sclerosis, although there might be biases and sources of error in the statistics. We should like to ascertain this problem by the further epidemiologic survey in the selected communities in Japan.

SUMMARY

We have collected 270 cases of demyelinating diseases of unknown etiology from various sources in Japan; 6 were diagnosed as, or believed to be, multiple sclerosis clinically.

The clinical features of these multiple sclerosis cases were similar to those observed in clinical series from other countries. However, there is as yet no confirmed autopsied case of chronic multiple sclerosis in our series.

Among the 270 cases, 175 were diagnosed as, or believed to be, neuromyelitis optica, a large number when compared to the number of multiple sclerosis. Among these patients, 29 died; autopsy findings in 18 were compatible with neuromyelitis optica.

Incidence of multiple sclerosis, neuromyelitis optica, and other unclassified demyelinating diseases among the neurologic admissions in the Tokyo University Hospital is 0.1, 0.6, and 0.2% respectively. The incidence of multiple sclerosis is supposed to be less than in the United States and European countries.

Most cases of neuromyelitis optica remitted or recovered and the course was usually long. In some patients, the brain or brain stem was involved. The clinical and pathologic features of our cases of neuromyelitis optica might be similar to those of the other countries, with minor differences.

We are indebted to Drs. A. Liebow of Yale University and A. Wolf of Columbia University for autopsy material for comparative purposes, to Drs. Fred A. Mettler and Leonard T. Kurland for correction of the draft, and to the staffs of various medical schools and hospitals for their cooperation in this survey.

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■ The diagnosis of epilepsy is very clear. We are in no danger of confounding it with any other disease, unless it be hysteria, from which it may be distinguished by the foaming at the mouth, the gnashing of the teeth, the blackness of the countenance, and the terrific symptoms above detailed in its history, together with the speedy termination of the fit in sleep, and the absence of the usual symptoms of hysteria; such as the globus hystericus, the palpitation of the heart, the involuntary laughing or weeping, and the other symptoms generally described in the histories of that disease.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Critical flicker frequency and EEG findings in patients with brain damage

Kenneth A. Kooi, M.D., Reed S. Boswell, M.S., and Madison H. Thomas, M.D.

THE CLINICAL USE of the electroencephalogram, particularly in nonepileptic cerebral disorders, has been based largely upon empirical criteria; little attention has been given to possible functional relationships. The present study is an attempt to evaluate the degree of association, if any, that exists between critical flicker frequency – the frequency of an intermittent source of light at the point of subjective fusion – and electroencephalographic findings in patients with brain damage.

Occipital spontaneous rhythms and response to photic stimulation (photic "driving") have been selected for special study because of their apparent relationship to visual activities.

MATERIAL AND METHODS

Observations on 133 subjects, categorized into 1 control and 4 diagnostic groups, form the basis of this report. The number, average age, and age range of the subjects in each group are presented in table 1. Control subjects were hospital employees and college students. The psychiatric group consisted of elderly patients without evidence of neurologic disease; 14 had schizophrenia; 3, depressive reaction; 1, inadequate personality; and 1, psychosis of undetermined etiology. Ocular damage was not evident, but 1 patient had had electroconvulsive therapy ten months prior to testing. Patients with interim or final diagnoses indicating cerebral damage were subdivided into those with [1] neurologic signs of brain lesions, such as hemiparesis, homonymous hemianopsia, and sensory deficit: [2] chronic brain syndrome, evidenced by intellectual impairment only; and [3] ocular involvement in addition to cerebral damage. Patients with neurologic signs included 17 with conditions diagnosed as cerebral vascular accident; post-traumatic encephalopathy was the diagnosis of 4; paralysis agitans and chronic brain syndrome, 1; Huntington's chorea, 1; internal carotid aneurysm with subarachnoid hemorrhage, 1; and encephalitis, 1. The ocular damage group included 3 patients with optic atrophy, 3 with cataracts, 2 with optic atrophy and cataracts, 1 with glaucoma, 1 with alcoholic amblyopia, and 1 with multiple refractive bodies in retina.

The electroencephalograms were recorded with a Grass model III D instrument using frontal, central, temporal, and occipital scalp derivations. The occipital leads were each placed 4 cm. above and 4 cm. lateral to the external occipital protuberance. Recordings of not less than ten minutes' duration, incorporating both scalp-ear and scalp-scalp electrode combinations were obtained on all subjects. The occipital basic frequencies were established for each hemisphere by averaging counts of 10 one-second samples taken from the initial and final routine scalp-ear runs.

Photic stimulation at 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, and 30 cycles per second was carried out with a Grass PS-1 photostimulator set at intermediate intensity. The cortical responses to photic stimulation were quantified with an Offner frequency analyzer, type 830. The details of the technic of photic stimulation and electronic analysis have been previously outlined.[1]

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TABLE 1
CRITICAL FLICKER FREQUENCIES IN 133 SUBJECTS IN 5 DIAGNOSTIC GROUPS

			Cerebral Damage		
	Control subjects	*Psychiatric, no neurologic disease*	*Chronic brain syndrome, intellectual impairment*	*Neurologic signs of brain lesions*	*Concomitant ocular damage*
Number of subjects	60	19	18	25	11
Average age	31	63	64	54	64
Age range	18–52	58–67	47–86	34–70	22–86
Average critical flicker frequency*	32	28.5	25.5	25	22.5
Flicker frequency range*	25–38	13.5–31.5	15–31	11.5–35	16–28

*Cycles per second.

The critical frequency of flicker was obtained for each subject on the day of electroencephalographic examination, except in rare cases within the control group. An electronic apparatus, consisting of an Ensco FF-114 square wave generator driving a Sylvania R1130B crater type, glow modulator lamp house in a separate viewer, was employed. Since the signal generator produced a square wave driving pulse and the firing time of the lamp was practically instantaneous, a constant 1:1 light-dark ratio was maintained for all frequencies. A 7-in. vernier dial permitted accurate frequency settings.

The light from the glow modulator was passed through an opal glass diffusion screen covered by a black mask with a circular, 4-mm. opening at its center. The intensity of the stimulus patch at this opening was .44 millilamberts as measured by the McBeth Illuminometer. The stimulus patch observed by the subject was 32.4 cm. from the corneal surface of the eyes and subtended a visual angle of forty-two minutes. The calculated diameter of the image at the retina was well within the limits of the fovea.

Each subject was dark-adapted for five to ten minutes and then given a brief training session, during which an approximate critical flicker frequency was established. An automatic timer allowed the stimulus light to be on and off for seven-second intervals for each frequency setting. During the off interval, the subject reported his reaction as flicker or steady, or their equivalents. Reliable discriminations of one-half cycle per second were made by all the subjects. Using the method of random trials, 10 critical flicker frequency values were obtained. The mean of the 10 trials was used in the statistical analyses.

RESULTS

Group findings. The averages and ranges of the critical flicker frequencies for the groups studied are presented in Table 1. The mean of the normal control group was significantly different, beyond the 1% level of confidence, from the mean of each of the other groups. The differences between the means of the psychiatric and brain-damaged groups were also highly significant, those between the psychiatric group and the neurologic and ocular damage groups being beyond the 1% level and that between the psychiatric and chronic brain syndrome groups at the 2% level. The range of critical flicker frequency values of each group indicates a high degree of overlapping. With the technic used for the determination of the critical flicker frequencies in this study, values below 25 cycles per second were considered highly indicative of organic cerebral dysfunction in the absence of ocular damage. No normal control subject had a critical flicker frequency below 25, and 2 subjects in the psychiatric group had readings of 13.5 and 24.5 cycles per second. The percentages of subjects with findings below 25 cycles per second in the chronic brain syndrome and neurologic groups were 30 and 40%, respectively.

TABLE 2

ELECTROENCEPHALOGRAPHIC CLASSIFICATIONS VERSUS CRITICAL FLICKER FREQUENCIES IN PATIENTS WITH CEREBRAL DAMAGE*

	Normal	*Abnormal, occipital frequencies above 8.5 cycles per second*	*Abnormal, occipital frequencies below 8.5 cycles per second bilaterally*
Number of subjects	10	9	12
Average age	60	59	60
Age range	36–76	36–63	37–68
Average critical flicker frequency†	27	27	23
Flicker frequency range†	24–31	21–29	11.5–30

*Cases with low voltage fast and dissimilar basic patterns, 1 above and 1 below 8.5 cycles per second over the two hemispheres, were excluded from the tabulation.
†Cycles per second.

Electroencephalographic findings. The patients with brain damage were further studied in order to assess the relationship between various types of electroencephalographic abnormalities and lowering of fusion frequencies. The results are shown in table 2. Those patients with cerebral damage and normal electroencephalograms or abnormal electroencephalograms with occipital frequencies within the normal range bilaterally were found to have fusion frequencies averaging significantly higher than those in patients with bilateral slowing in occipital regions. In spite of the small size of these groups, these differences were both significant at the 5% level of confidence. Electroencephalographic abnormality, other than occipital slowing, did not appear to increase the possibility of low flicker fusion frequency findings as the identical averages of the first 2 groups reveal. On the other hand, fusion frequencies were not invariably low in the presence of occipital patterns below 8.5 cycles per second; critical flicker frequency values of 26.5 to 30 cycles per second were noted in 4 cases. The relationship between occipital basic frequencies and critical flicker frequency values was also determined by computing the product-moment correlation between these variables after all cases with unequal basic frequencies for the 2 hemispheres and uncountable patterns were excluded. For the remaining 28 cases, with age held constant, a correlation coefficient of + .52 was found which is significant beyond the 1% level of confidence for the sample size.

Additional evidence that the occipital rhythm and the fusion frequency are related variables is obtained from examining the average critical flicker frequencies of 6 brain-damaged patients with ocular damage and basic occipital frequencies below 8.5 versus 4 with frequencies above 8.5 cycles per second; averages were 21.5 and 24.5, respectively. Because of a variable occipital frequency, 1 subject was omitted from this comparison. All electroencephalograms were abnormal in this group of patients.

Homonymous hemianopsia was diagnosed in 3 patients, none of whom were in the group with bilateral occipital slowing. A critical flicker frequency of 28 cycles per second was noted in 1 patient with a bilateral alpha rhythm of 11 cycles per second. The frequency of the basic pattern was below 8.5 cycles per second over the damaged hemisphere in the other 2 patients and critical flicker frequencies of 14 and 22 cycles per second were obtained.

Product-moment correlations between occipital and critical flicker frequencies computed for 2 normal control groups, of 27 and 26 subjects each, were + .23 and + .11, respectively; neither of these values were significant at the 10% level of confidence. A correlation of + .01 was found for 18 psychiatric patients. Those subjects who had low voltage, fast records were excluded in each case. No significant difference between the means of fusion frequencies of 7 subjects with low voltage, fast patterns and the remaining subjects with predominantly alpha patterns was observed. Con-

trol subjects with low voltage, fast patterns had fusion frequencies ranging from 26 to 38 cycles per second, with an average of 31.5. Friedl[2] and Dondero, Hofstaetter, and O'Conner[3] have previously reported very low correlation coefficients between alpha index and critical flicker frequency.

Photic stimulation. Scores representing the amplitude and persistence of the occipital response at the fundamental of the photic stimulus frequency in 30 control and 41 brain-damaged subjects were obtained from the analyzer writeout for 4 ranges of stimulation – 2 and 3; 4 and 6; 8, 10, and 12; and 16, 20, 24, and 30 cycles per second. Above- and below-average fusion frequencies and photic response scores for each range were compared. The hemispheres were treated separately in the organic group. None of the differences were statistically significant.

DISCUSSION

The frequent reduction of the critical flicker frequency in patients with brain damage is well established. To our findings may be added those of Werner and Thuma,[4] Halstead,[5] Phillips,[6] Battersby,[7] Miles,[8] Irvine,[9] Ax and Colley,[10] Stauffacher, Marks and Ax,[11] and Parsons and Miller.[12] On the other hand, many individuals with known cerebral lesions have been found to have fusion thresholds within the normal range. The electroencephalographic findings suggest that the type of cerebral dysfunction may differ in those with high and low crtiical flicker frequency values. When the cerebral disturbance is such that interference with occipital electrocortical patterns occurs, a low fusion frequency may be expected more often than if other types of electroencephalographic abnormalities are present; in fact, abnormalities other than those in which a slowing of the alpha rhythm might reasonably be inferred did not increase the tendency toward lower critical flicker frequency values in subjects with organic damage.

In spite of the substantial correlation between fusion and occipital frequencies in patients with cerebral disorders, many individual exceptions were noted. It is not possible to fully elucidate the reasons for these exceptions at present, but such factors as the wide range of normal fusion values, the lack of significant correlation between critical flicker frequency values and alpha frequencies in control subjects, and the probability that similar occipital rhythms are not functionally equivalent must be considered. Chyatte[13] and Lindsley and Lansing[14] also have reported that alpha and critical flicker frequency are not significantly related phenomena in normal subjects. This suggests that alpha frequency does not normally determine the level of critical flicker frequency but that cerebral disorders may often alter both in the same direction.

The complete lack of correlation between critical flicker frequency values and cerebral responses to photic stimulation was unexpected inasmuch as it was previously shown that a reduction of photic responses in the range of 16 to 30 cycles per second occurred in patients with slow occipital rhythms.[1] However, it should be pointed out that photic responses are complex and consequently difficult to quantify. Further investigation in this area is indicated.

SUMMARY AND CONCLUSIONS

Critical frequencies of flicker have been obtained in 133 subjects and studied in relation to diagnostic categories and electroencephalographic findings. The following observations were made:

1. Average flicker frequencies were significantly lower in 2 groups of patients with clinical evidence of brain damage, without ocular involvement, than in either the young normal or elderly psychiatric control groups.

2. In those patients with brain damage, the type of electroencephalographic abnormality was found to be a significant variable. Thus, critical flicker frequency positively correlated with the frequency of the occipital basic pattern. On the other hand, flicker frequencies of brain-damaged patients with abnormal electroencephalograms but with occipital rhythms within the normal range were not lower than those of patients with normal electroencephalographic tracings; furthermore, the average flicker frequencies of the brain-damaged patients with normal or abnormal electroencephalograms, without appreciable alteration of occipital rhythms, were not significantly different from the average of the group of elderly psychiatric patients.

3. No significant relationship was found between critical flicker and alpha frequencies in the normal control or psychiatric groups.

4. A small group of normal subjects with a low alpha incidence exhibited no observable increased tendency to have low fusion frequencies.

5. Cerebral responses to photic stimulation as measured in the present study were not related to critical flicker frequencies.

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A new drug for petit mal epilepsy

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A NEW COMPOUND in the treatment of petit mal epilepsy, a-ethyl-a-methylsuccinimide, is the third evolving from our investigation into the treatment of this condition, and, like its predecessors – Milontin (methylphenylsuccinimide) and Celontin (N-methyl-a, a-methylphenylsuccinimide) – it is also a member of the new succinimide chemical series.

When this research was begun about ten years ago, only two compounds existed which could make any serious claims to effectiveness against petit mal attacks – phenobarbital and trimethadione (Tridione). Any other drug existing at that time had at best only a fringe effect on petit mal epilepsy. Phenobarbital has a limited, but broad spectrum, effect on grand mal, petit mal, and other types of epilepsy. It is probably for this reason that the drug persists as a mainstay in the armamentarium of many physicians today, in spite of its known obtunding effect on mentation. Tridione, on the other hand, has a brilliant and dramatic effect upon petit mal epilepsy, but its unpredictable, though rare, property of causing death from blood changes does not augur well for the peace of mind of the physician. Its other side effects like photophobia and rash are, like the side effects of other drugs, disconcerting, but bearable and not serious.

The need for new and better drugs to treat petit mal epilepsy was great. Our therapeutic goal, naturally, was to evolve a compound equal or superior to Tridione, without its grave side effects. Put in another way, our aim was to avoid paying a high therapeutic price for a high therapeutic goal. This is a pharmacologic tight rope balancing feat since it is well known that toxicity frequently tends to increase with therapeutic effectiveness.

The first drug evolved was, as is often the case, a therapeutic compromise in the interest of safety. Milontin had the virtues of complete safety and mild or innocuous side effects; the necessity of high dosage levels to achieve a good therapeutic effect, however, proved to be a disadvantage which, in turn, led to a secondary psychologic disadvantage. Most parents are impatient for an immediate therapeutic effect; the need to increase the dosage slowly up to the necessary effective level without the sudden, dramatic reduction in attacks elicited with Tridione often proved discouraging to parents and, probably, to the doctor himself at times.

Further, people are quite prone to feel that the more medicine required, the more chance there is for a serious toxic reaction. This mental attitude acts as a deterrent to parental cooperation, vitally needed by the physician. In that respect, Milontin has stood the test of time in the mildness of its side effects and is therefore still the drug of choice.

Celontin, the second drug evolved, grew out of our efforts to find a faster acting, but still not seriously toxic, medication. This drug, we feel, will become an invaluable addition to the therapeutic armamentarium in the treatment of epilepsy when its effectiveness is more generally known. Coincidentally, in contrast to Milontin, we found it had a broad spectrum of activity; it is the only drug we know that has a high degree of effectiveness against [1] psychomotor attacks, [2] petit mal attacks with a psychomotor element, and [3] the frequently seen mixed type of attack that defies proper classification. The therapeutic price, while greater than Milontin, is still not serious and has caused no blood dyscrasias in any of our patients over several years' observation.

A-ethyl-a-methylsuccinimide, hereafter designated by its laboratory number of PM 671, is the third compound and the subject of this

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The experimental succinimide compounds, Milontin, Celontin, and PM 671, were synthesized and developed in the laboratories of Parke, Davis and Company, Detroit.

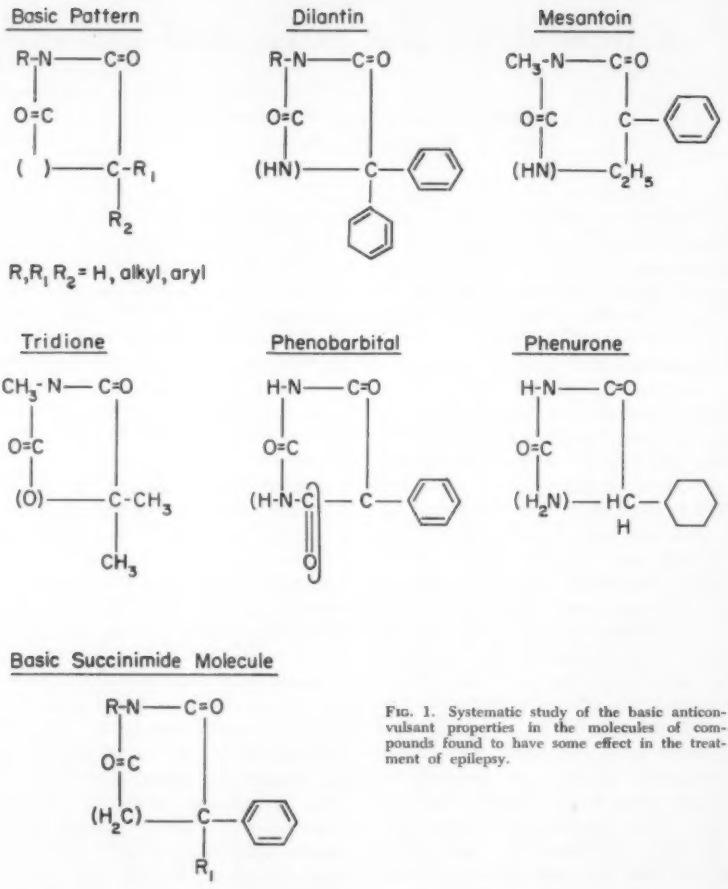

FIG. 1. Systematic study of the basic anticonvulsant properties in the molecules of compounds found to have some effect in the treatment of epilepsy.

preliminary report. To date, this appears most nearly to approach our original goal of a high and dramatic degree of effectiveness against pure petit mal epilepsy with a relatively low incidence of harmful side effects. Personal communications from Switzerland, Denmark, and North Carolina appear to bear this out.

CHEMICAL SYNTHESIS AND PHARMACOLOGY

As previously stated, this study began about ten years ago with a systematic study of the anticonvulsant properties of the chemical groups known to be at all effective in the treatment of epilepsy. Out of this study, a basic anticonvulsant complex appeared to emerge as part of the compound which latter may be an open chain or a heterocycle. This can readily be seen by an inspection of the molecules of phenobarbital, trimethadione, Dilantin, and Mesantoin (Fig. 1). After examining samples of the piperidine group – thiazolidine and furnanacrylamide – and the cinnanamide type – which were discarded because of their toxic manifestations – the succinimide group appeared to hold the most promise in terms of effectiveness and reduced toxicity.

This basic succinimide molecule was then

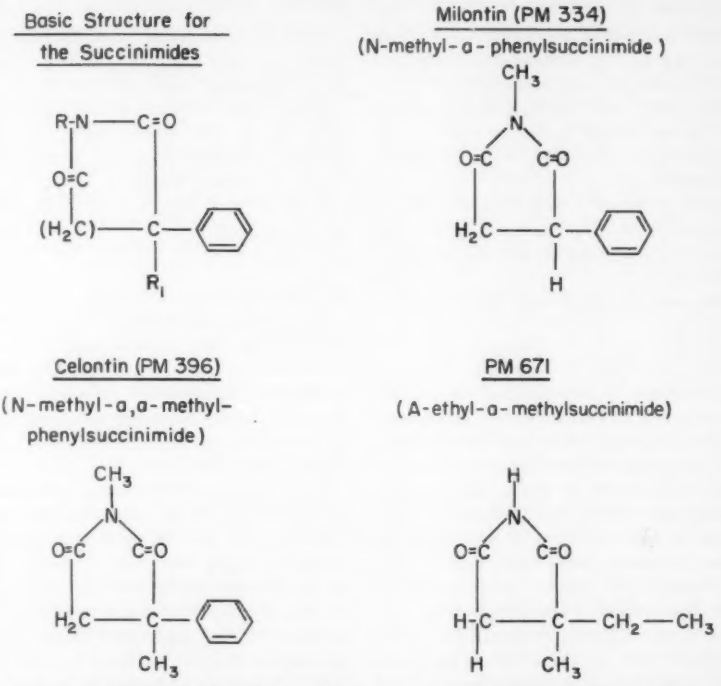

FIG. 2. The basic succinimide molecule and alterations in it resulting in the synthesis of Milontin, Celontin, and PM 671.

altered systematically. The alterations resulting in the synthesis of Milontin (PM 334), Celontin (PM 396), and PM 671 are given in figure 2. In synthesizing PM 671, an ethyl group was substituted for a phenyl ring at the No. 3 position and a methyl group for hydrogen in the same No. 3 position. The remainder of the molecule is identical with Milontin. When comparing Celontin, which is particularly effective against psychomotor attacks, with the molecule of PM 671 and Milontin, the difference in clinical action of Celontin, with its broader spectrum toward the grand mal end of the scale, seems to depend upon the phenyl ring in the No. 3 position rather than the ethyl group as in the molecule of PM 671. In the case of Celontin, animal studies indicated a much higher degree of control of petit mal attacks than PM-671 results suggested; this was not borne out clinically.

ANIMAL STUDIES

PM 671 was selected for clinical trial, as were Milontin and Celontin, on the basis of its protective action against Metrazol-induced convulsions in animals. A dose of 125 mg. per kilogram of body weight was effective in protecting rats against the convulsant action of pentylenetrazol (Metrazol) – a 500-mg. dose of Tridione was required.

Toxicity studies indicated that mice fed PM 671 in the diet for five weeks tolerated the ingestion of 120 mg. per kilogram of body weight daily with normal weight gain. Monkeys tolerated 300 mg. per kilogram of body weight reasonably well. Biochemical, hematologic, and urinary findings remained in the normal range. Clinically, during the three-year pilot study of this drug, all blood and urine determinations remained normal.

CLASSIFICATION OF ATTACKS

All cases included in this study were classified according to the system of classification previously developed and reported:[1]

1] Pure petit mal (pyknoepilepsy) – that form of epilepsy which manifests itself in loss of consciousness only, with no concomitant motor phenomena.

2] Mixed petit mal – that form of epilepsy which manifests itself predominantly in transient loss of consciousness and minor motor phenomena.

3] Petit mal combined with other types of seizures.

MATERIALS AND METHODS

This preliminary report is based on a study of 109 cases of petit mal treated in the seizure section of Vanderbilt Clinic and the Division of Child Neurology of the Neurological Institute. Over the years of study with various drugs in the same clinic and with a good percentage of the same patients, it may safely be said that a relatively hard core of intractable cases is represented. Many new cases have, of course, been added from time to time.

Electroencephalographic confirmation of clinical diagnosis was always sought, but cases were not discarded if confirmation did not occur; if the recognized clinical criteria of petit mal were present in such cases, they were included in the study.

Attacks were recorded by the child's parents on a calendar sheet previously described and reported. The sheet was brought to the clinic with each visit and transcribed on a permanent record which was put in continuous graph form each week.

DOSAGE

PM 671 was given orally in 0.25-gm. capsules. The initial dose was 1 or 2 capsules per day, depending upon the age of the patient; children under 6 years of age were given only one capsule per day initially. Dosage was gradually increased over a period of weeks until an optimal dosage level was reached or until toxic side effects intervened. The average daily dose was 1.75 gm., or 7 capsules per day.

RESULTS

In previous publications,[2,3] the various types of base lines used in measuring drug effectiveness were reported. In this study, the action of the drug immediately preceding administration of PM 671 was taken as a base line. This is the most rigid of all the methods of measurement possible.

Petit mal cases responded remarkably well to PM 671, with an over-all reduction in attacks of 85% for the group as a whole for periods ranging from ten to ninety-six weeks or an average of thirty-seven weeks. Results of PM 671 in the treatment of petit mal attacks, with the high percentages of control indicated, are given in detail in table 1. Complete control was secured in 42% of the patients, for an average of forty-four weeks. Practical control was reached in 24% of the cases and partial control in 26%, making a total of 92% of all patients treated receiving some benefit from the drug. No results, or an increase in attacks after medication, occurred in only 8% of patients receiving PM 671.

Because some benefit was reported with Celontin,[3] it was decided to see whether the

TABLE 1

EFFECTIVENESS OF PM 671 IN CONTROLLING OR REDUCING PETIT MAL ATTACKS IN CHRONOLOGIC CONTINUITY IN 109 PATIENTS

	Number of patients	*Per cent*	*Average duration of treatment (weeks)*	*Range of control (weeks)*
Complete control	46	42	44	12 to 96
Practical control (80 to 99% reduction)	26	24	82	71 to 89
Partial control (5 to 79% reduction)	28	26	43	18 to 49
No effect (0 to 4% reduction)	7	6	34	20 to 43
Increased attacks	2	2	7	3 to 20

use of Celontin immediately before PM 671 influenced results in favor of the latter by providing a stepping stone from an originally higher base line. This did not prove to be the case, however. All 7 cases benefited from treatment with PM 671, whereas no medication including Celontin previous to the time PM 671 was given had provided any favorable effect whatsoever on petit mal attacks. Reductions in attacks on PM 671 after Celontin for these 7 intractable cases are given in table 2.

In order to determine the effect of PM 671 on petit mal attacks in patients with more than one type of seizure, cases were divided according to diagnosis. The results are shown in table 3; it is clear that PM 671 was much more effective in the treatment of pure petit mal than other types of seizures combined with mixed petit mal. Complete control, for example, was reached in 61% of the pure petit mal cases, as compared with only 21% among patients having mixed petit mal. When pure petit mal occurred with grand mal, 59% of the cases were completely controlled; in contrast, only 35% of patients having a combination of mixed petit mal and grand mal were completely controlled. If the categories of complete and practical control are considered together, 83% of all pure petit mal cases reached high levels of control; only 29.5% of the mixed petit mal patients are included. When pure petit mal was combined with grand mal, 90% of patients fell within the practical or complete control categories, that is, after treatment with PM 671, they reached a reduction of at least 80% in number of attacks. On the other hand, only 70% of the mixed petit mal and grand mal cases succeeded in obtaining this high degree of control when both types of attacks existed simultaneously.

Clinical experience so far with PM 671 indicates that it is essentially a petit mal drug. At times it seemed that a few cases having grand mal attacks benefited from the drug, but the evidence is inconclusive and outweighed by the fact that grand mal attacks were definitely aggravated, as is often the case with a petit mal drug, in certain instances, particularly when insufficient grand mal medication was given.

Sometimes, effectiveness of medication is related to frequency of attacks. Findings were therefore considered from the point of view of number of attacks which existed at the beginning of PM-671 treatment in order to see whether frequency of petit mal attacks was correlated with the action of the drug, directly or inversely. The results are shown in table 4. On the basis of these findings, there does not seem to be a relationship among the patients studied between average number of petit mal attacks before treatment and the effectiveness of PM 671 in controlling or reducing petit mal attacks.

Regardless of what medication is given, we have noticed, over several years, that many patients tend to develop a tolerance to a particular drug when it is given for any length of time. Once this saturation point is reached, degree of previous control begins to diminish and it is necessary to introduce other medication to maintain former gains. Any drug that maintains control over extended intervals of time would, therefore, have a distinct advantage over those that maintain effectiveness for

TABLE 2

STUDY OF 7 PETIT MAL CASES RECEIVING NO HELP FROM BASE LINE CELONTIN THERAPY, WHO RESPONDED FAVORABLY TO PM 671 ADMINISTRATION

	Celontin		*PM 671*	
	Number of patients	*Per cent*	*Number of patients*	*Per cent*
Complete control	0	0	3	43
Practical control (80 to 99% reduction)	0	0	2	28.5
Partial control (5 to 79% reduction)	0	0	2	28.5
No effect (0 to 4% reduction) or increased attacks	7	100	0	0

TABLE 3

EFFECTIVENESS OF PM 671 IN THE TREATMENT OF PETIT MAL ATTACKS IN 109 PATIENTS WITH MORE THAN ONE TYPE OF SEIZURE

	Pure petit mal		*Mixed petit mal*		*Pure petit mal and grand mal*		*Mixed petit mal and grand mal*		*Pure petit mal and psychomotor*		*Pure petit mal, grand mal, and psychomotor*	
	Number of patients	*Per cent*	*Number of patients*	*Per cent*	*Number of patients*	*Per cent*	*Number of patients*	*Per cent*	*Number of patients*	*Per cent*	*Number of patients*	*Per cent*
Complete control	11	61	5	21	17	59	9	35	2	29	2	40
Practical control (80 to 99% reduction)	4	22	2	8.5	9	31	9	35	1	14	1	20
Partial control (5 to 79% reduction)	3	17	14	58	2	7	3	11	4	57	2	40
No effect (0 to 4% reduction)	0	0	2	8.5	1	3	4	15	0	0	0	0
Increased attacks	0	0	1	4	0	0	1	4	0	0	0	0
	—		—		—		—		—		—	
Total	18		24		29		26		7		5	

TABLE 4

RESULTS DIVIDED ACCORDING TO NUMBER OF PETIT MAL ATTACKS BEFORE TREATMENT WITH PM 671

	Number of patients	*Average number of attacks per week before treatment*
Complete control	46	14
Practical control (80 to 99% reduction)	26	12
Partial control (5 to 79% reduction)	28	49
No effect (0 to 4% reduction)	7	13
Increased attacks	2	22

shorter periods. Findings to date with PM 671 indicate that it has much better holding action than standard medications. The category of complete control is considered for six-month intervals up to and including two years of treatment in table 5.

Our studies show that the percentages of complete control for cases treated with all drugs except PM 671 dropped consistently over a period of time. In contrast to these findings, percentages of complete control for PM 671 have risen from 28% after six months of treatment to 42% at the end of the two-year interval. Results to date unquestionably favor the action of PM 671 as far as ability to hold former gains is concerned.

Regardless of anticonvulsant action, it is necessary to consider incidence and nature of toxic side effects in evaluating petit mal medication. All during our research, priority has been given to the safety of drug therapy – preference being shown for drugs with mild and infrequent side reactions over those having excellent therapeutic action at the expense of distressing or dangerous side effects. Mildness of side reactions, in fact, has been one of the distinct advantages of the whole succinimide group over other standard and experimental petit mal medications. No blood dyscrasias have been encountered.

Toxic side reactions on PM 671 have occurred in only 9% of all patients treated. These side effects usually appeared on relatively high dosage levels and could be reduced or elim-

TABLE 5
DURATION OF EFFECTIVENESS OF DRUGS AFFORDING COMPLETE CONTROL OF PETIT MAL ATTACKS

	Complete Control for:			
	6 months (Per cent of cases)	*1 year (Per cent of cases)*	*18 months (Per cent of cases)*	*2 years (Per cent of cases)*
Phenobarbital	22	17	11	8
Tridione	36	34	31	28
Milontin	30	27	24	21
Celontin	22	20	19	19
PM 671	28	34	39	42

inated entirely in most cases by a reduction in the amount of medication given. Blood and urinary findings remained within normal limits. Nature and incidence of toxic side effects are shown in table 6.

TABLE 6
NATURE AND INCIDENCE OF TOXIC SIDE EFFECTS WITH PM 671 IN 109 CASES

Side effect	*Number of patients*
Drowsiness	4
Dizziness	2
Nausea	2
Gastric distress	2

SUMMARY

This article reports upon the effect of PM 671 in controlling or reducing petit mal attacks in 109 patients, many of whom were considered intractable cases.

The present drug, PM 671, on the basis of effectiveness against petit mal attacks, mildness of side effects, and holding ability, offers more promise than other succinimide compounds and medications tested in the past ten years.

Quick and dramatic reduction of attacks occurred in most of 109 patients studied, and side effects were mild and infrequent. Side reactions were occasional drowsiness and dizziness, with some nausea and gastric distress – usually on high doses. Nausea and gastric distress are basic side effects to all succinimide compounds, but, fortunately, they are rare and not particularly disturbing. No deleterious changes in the blood picture have been noted to date, and urinary findings are within normal limits. No skin rashes have been noted.

Studies revealed that PM 671 is also outstanding in the lack of "slippage"– that property in a drug of slowly losing its holding power. Quite a few patients, never before helped by any drug, have been completely controlled for several years on PM 671.

For the group as a whole, an over-all 85% reduction in attacks was obtained in the treatment of petit mal epilepsy. Complete control of petit mal attacks was secured in 42% of patients treated; practical control with an 80 to 99% reduction in attacks in 24%; and partial control, 5 to 79% reduction, in 26%.

Experience to date indicates that PM 671 is essentially a petit mal drug. Much more effectiveness was noted in the treatment of pure petit mal cases – where pure petit mal existed alone or was combined with other types of seizures – than when a "mixed" petit mal element was present. Results showed that 83% of all pure petit mal cases had a reduction in attacks of at least 80% after therapy; only 29.5% of the mixed petit mal cases reached this high level of control. The individual frequency of attacks likewise did not appear to have any relation to the effectiveness of medication.

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The fate of offspring from mothers receiving sodium pentobarbital before delivery

A study in the guinea pig

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OVERSEDATION of the pregnant mother with barbiturates administered near term has been postulated as a possible etiologic factor in fetal brain damage. This has been partially predicated upon the observation[1–3] that experimentally induced hypoxia in utero, effected by clamping uterine vessels in the pregnant guinea pig near term, can lead to spastic paralysis and other neurologic aberrations in the newborn young. Eight to twelve weeks after birth, many of the surviving young showed striking deficits in learning ability and retentive capacities. Brains of such offspring, sacrificed at various postnatal intervals, demonstrated considerable residual neuropathology. None of these disturbances appeared in litter-mate controls delivered from the same mothers before induction of the hypoxic crisis.

The possibility exists that certain obstetric drugs, the barbiturates in particular, might well create adverse conditions in utero either by markedly depressing the fetal respiratory center directly or by interfering with the hemodynamics of blood flow across the placenta. To test this hypothesis, we administered sodium pentobarbital (Veterinary Nembutal) to pregnant guinea pigs near term.

METHOD

In our colony, full term ranged from sixty-four to seventy-two days, for an average of 66.5 days. Dosage level and injection date were preassigned by the method of true randomization at the time of mating in our own colony or when we received a pregnant pig from the outside. In our stock cages, nonpregnant pigs were placed with a male on the first day of observed vaginal membrane rupture and were left with the male for three days. The second of these days was arbitrarily selected as the most likely conception date. Pregnancy could be confirmed by palpation eighteen to twenty days after this date if membrane rupture did not recur within that interval. With this method, we were not more than two days off in setting injection dates or in calculating due dates for deliveries.

Two chief approaches were used – one of drugged cesarean delivery and the other of drugged natural delivery.

Cesarean delivery. After a sixty-five-day gestation period, pregnant guinea pigs were delivered in an isotonic, constant-temperature bath of Locke's solution. After local infiltration of the maternal abdomen with xylocaine, a control animal was delivered. Then, the mother was given sodium pentobarbital by cardiac puncture. The dosage level administered was either light, 28 mg. per kilogram, or heavy, 40 mg. per kilogram. The effect of the drug upon fetal behavior was observed while the exposed gravid uterus remained immersed in the water bath. The anesthetized experimental animals were delivered at time intervals varying from either one to five minutes after cessation of fetal respiratory-like activity in utero or twenty minutes after drug administration when no respiratory-like efforts were observed.

Drugged natural delivery. The drug was given intraperitoneally to the intact pregnant

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mother, who was then allowed to deliver normally after recovery from anesthesia. The light dose for these animals, 30 mg. per kilogram, was 10% lethal as predetermined in 40 animals, and the heavy dose, 38 mg. per kilogram, was 40% lethal. A control group of mothers was given a placebo injection of 0.5 cc. of saline on the sixty-third day of gestation. The light and heavy drug dosages were administered at 3 time intervals during gestation – the twenty-second, forty-second, and sixty-third days. These intervals were chosen to represent periods when: [1] early cord reflexes were developing; [2] larger patterns of fetal behavior were being integrated; and [3] neural pathways were well myelinated.

An additional control group of 11 litters of noninjected, normally born young served for comparative purposes.

It should be noted that when these experiments were conducted, housing for guinea pigs was not as ideal as it is now. The stock room in which our guinea pigs were kept held other assorted species of animals; summer temperature and humidity varied widely, and guinea pigs were procured in job lots from local dealers. There were no standardized animals raised under standard conditions. Disease brought in by other species or by job-lot procurement was hard to control. Our present dietary control had not been worked out, and animals were fed an unrestricted fare of Purina Guinea Pig Diet, water, and a thrice weekly cabbage supplement. We have since learned[4,5] that this was not the choicest regime for assuring good growth and reproduction in guinea pigs.

TABLE 1
CONTROL GROUPS

Data	*Cesarean controls (Litter-mate controls)*	*Normal births*
Controls	17	16
Average litter size	2.6	2.3
Sex	M 5 F 12	M 8 F 8
Average birth weight (gm.)	M 88.0 F 83.0 > 85.0	M 81.9 F 76.4 > 79.1
Survival	12 three months* 5 < one week	12 three months* 4 < one week

* Length of observation period.

RESULTS

Cesarean delivery. The behavior of 17 water-bath, nondrugged cesarean controls and of 16 normally born neonates was compared with that of 20 drugged, cesarean neonates. Table 1 shows that there were no fundamental differences between the two control groups in terms of birth weight, litter size, or survival over the three months' observation period. The slight birth weight advantage noticed in the cesarean-delivered group was entirely within the realm of sampling error. Variation about mean birth weight values was large in both control groups. Behaviorally, the two control groups were also alike in that no animal in either group exhibited symptoms of neural damage. This was in marked contrast to the findings in drugged deliveries.

Table 2 compares [1] the cesarean-delivered experimental animals with their own litter-mate controls and [2] the lightly and heavily anesthetized groups with each other. While

TABLE 2
CESAREAN DELIVERIES: DRUGGED VERSUS CONTROL GROUPS

Data	*Light dose*		*Heavy dose*	
	Experimental	*Control*	*Experimental*	*Control*
Dosage Nembutal (mg./kg.)	28	0	40	0
Drug action time (min.)	8.5	0	11.6	0
Animals delivered	13	12	7	5
Average number per litter	2.65		1.75	
Average birth weight (gm.)	88.6	83.6	84.7	80.5
Average duration of intrauterine respiration (min.)	4.2 (in 54%)	0	4.9 (in 86%)	0
Average duration of postnatal apnea (min.)	9.9 (in 54%)	0.05 (in 15%)	8.8 (in 100%)	0
Number requiring resuscitation	3	0	7	0

the experimental animals were actually heavier on the average at birth, they failed to recover their birth weight as rapidly as the controls during the first weeks of life.

Total exposure time to the anesthetic drug in utero varied from litter to litter but averaged eight and one-half minutes for the lightly anesthetized group and eleven and six-tenths minutes for the heavy dose group. Exposure times to Nembutal were not kept equal, as it was our practice to deliver fetuses after the last intrauterine gasp, and, when animals failed to exhibit early respiratory-like behavior in utero, we delayed delivery somewhat to allow for the possible late onset of such activity.

Intrauterine respiratory-like efforts of fetuses were clearly noted in 54% of the lightly anesthetized animals and in 86% of those heavily anesthetized. This ran counter to our expectations, for we had anticipated that the drug would probably depress the fetal respiratory center to such a degree that it would inhibit intrauterine respiratory-like behavior completely. The duration of intrauterine respiratory activity was approximately four and one-half minutes, regardless of the dosage level employed. The rhythmic nature of these thoracic cage excursions, sometimes shallow and sometimes deep and accompanied by gasplike mouth opening, could not be confused with other forms of fetal motility. Of the drugged fetuses, 7 failed to exhibit this type of behavior even after a twenty-minute exposure to Nembutal. In the other cases, it began within ten minutes of drug administration.

Postnatal apnea periods ranged from one-half to twenty-five minutes in the drugged neonates. Of the lightly anesthetized group, 7 failed to breathe at once, but only 3 of these required resuscitation. All of the heavily anesthetized animals were apneic at birth, and all required resuscitation in order to survive. Resuscitation was accomplished under positive pressure with oxygen from a regulated cylinder led into the trachea via a hypodermic needle.

Table 3 lists 11 common findings encountered in drugged neonates during their recovery phase. None of these symptoms was observed in the control animals, but all drugged survivors exhibited one or more of them—some showing more symptomatology than others. Severity did not correlate with dosage level or with Nembutal exposure time. Percentagewise, less symptomatology was observed in the lightly anesthetized group. Still, some animals in this group were afflicted with 6 or 7 of these disturbances or with as many in combination as were noted for the 3 worst affected in the heavily anesthetized group.

TABLE 3
FREQUENCY OF NEUROLOGIC SEQUELAE IN NEONATES DRUGGED DURING DELIVERY

Finding	*Light dose 28 mg./kg.*	*Heavy dose 40 mg./kg.*
Animals delivered	13	7
Atonia and cyanosis at birth	7 (54%)	7 (100%)
Delayed righting	9 (69%)	7 (100%)
Spastic limbs	5 (39%)	4 (57%)
Head and trunk tremors	7 (54%)	7 (100%)
Incoordinate gait	6 (46%)	4 (57%)
Alternate running movements	4 (31%)	2 (29%)
Failure to walk	2 (15%)	3 (43%)
Loss of startle reflex	4 (31%)	3 (43%)
Feeding problems	4 (31%)	3 (43%)
Piloerection	4 (31%)	2 (29%)
Forced circling	1 (8%)	0

While atonia and cyanosis were common findings at birth, certain animals nevertheless exhibited remarkable tone and breathed at once. It was felt that the recovery should be as uneventful as in the case of the littermate controls; yet, two or three hours later, they showed symptoms as severe as some of the atonic, apneic animals that had required resuscitation. Good muscle tone and the establishment of spontaneous respiration at birth in no way guaranteed an uneventful prognosis.

Most animals were delayed in righting efforts for an average of at least three to four hours. Controls righted as soon as they were born. More than one-third of the drugged animals developed spastic limbs and opisthotonos. Before righting, spasticity was more pronounced in the fore limbs than in the hind limbs. When locomotor efforts began, residual spasticity was greater in the hind limbs, resulting in awkward and incoordinate gaits. The animals walked stiff-legged, with the hindquarters carried high. They stepped on their own feet and stumbled. Some failed to walk at all, in which case they died within the first week of life. One specimen propelled itself along with its fore limbs while its lower

extremities dragged behind in rigid extension.

Spasticity often gave way to rapid, alternate running behavior with the animal lying on its side unable to right. These episodes of coordinate running appeared sporadically and often lasted for twenty minutes or more, leaving the animal completely exhausted.

Head and trunk tremors were marked. Less frequent findings were: forced circling; loss of startle reflex; and feeding difficulties because of cranial nerve paralyses to face, tongue, or pharynx. When inactive, many animals sat in peculiar hunched postures with the fur in marked piloerection.

Drugged natural delivery. On the twenty-second, forty-second, or sixty-third day of gestation, 24 pregnant guinea pigs were injected with either a light or heavy dose of Nembutal. A placebo injection of sterile saline was given 6 others on the sixty-third day. All were allowed to bear their own young.

Tables 4 and 5 show that 18 young were born in the placebo group, with no mothers dying; 27 young were born in the light dose group, with 4 mothers dying before term; and 29 young were born in the heavy dose category, with 5 mothers dying before term. The figures for young include stillborn and abortions as well as living young.

Survival at birth was not good—19% were living and 81% were stillborn or aborted in the lightly anesthetized group; 21% were living and the rest stillborn or aborted in the heavily anesthetized group. The placebo group had a

TABLE 4

TREATED ANIMALS ALLOWED TO BEAR YOUNG NORMALLY

Data	*Placebo (0.5 cc. Saline I.P.)*	*Light dose (30 mg./kg.)*	*Heavy dose (38 mg./kg.)*
Number of litters	6	13	11
Total young delivered	18	27	29
Average litter size	3	2.1	2.6
Number living at birth	9 (50%)	5 (19%)	6 (21%)
Average gestation (days)	66.1	66.5	64.8
Symptomatology	None	Slow weight gain	Spastic hind limbs Incoordinate gait Hunched posture Piloerection Slow weight gain
Survival	6 > 3 months* 3 < 1 day	5 > 3 months*	5 > 3 months* 1 < 1 day

* Three months = length of observation period.

TABLE 5

RELATION OF INJECTION DATE TO MORTALITY AT BIRTH

Data	*Placebo*	*Light dose (30 mg./kg.)*			*Heavy dose (38 mg./kg.)*		
Days gestation when injected	63	22-24	42-44	63	22-24	42-44	63
Average fetal age at delivery	67	59.5	67.25	64	——	65.5	65.5
Mothers injected	6	5	4	4	3	4	4
Mothers dying	0	2 (40%) (4 Fetuses)	2 (50%) (4 Fetuses)	0	3 (100%) (10 Fetuses)	2 (50%) (6 Fetuses)	0
Mothers aborting prematurely	2	2	0	0	0	1	0
Aborted fetuses	6	4	0	0	0	3	0
Term stillborn	3	1	1	8	0	0	4
Living young	9	0	3	2	0	2	4
Young surviving for more than 3 Months	6	0	3	2	0	2	3

50% survival rate at birth. Still, this latter rate was significantly better ($P = .02$) than for either of the drugged groups. During this phase of the study, respiratory infections were common in the stock colony. All animals were getting Sulmet in the drinking water in an effort to control the disease. The possibility exists that drugged animals could have been weakened and rendered more susceptible to the infectious organism than the control group.

Most of the animals surviving birth led a healthy life over the three months' observation period. The chief intergroup difference was the presence of a mild locomotor dysfunction in the young in the heavy-dose category. They all had noticeable rigidity in the hind limbs and walked with awkward, stiff-legged gaits. They often sat hunched and inactive. They were poor eaters requiring bottle supplementation. All lost considerable weight during the first two weeks of life.

None of these symptoms was observed in the placebo or lightly anesthetized groups, though the latter were slower to regain birth weights than were the controls.

No mothers injected on the sixty-third day of gestation died, but drug injections on this day yielded a high incidence of stillbirths – surprisingly more in the low- than in the high-dose category. Drug injections earlier in gestation resulted either in the death of the mother and litter before term or in a high rate of abortion with the mother surviving. There were no viable young from mothers injected on the twenty-second day and only 5 from those injected on the forty-second day.

DISCUSSION

Carmichael and Posey[6] set the median lethal dose for Nembutal in nonpregnant guinea pigs at 45 mg. per kilogram. None of our pregnant animals received a dose of this magnitude. Yet, in the case of drug administration to intact mothers allowed to bear their own young, the maternal death rate was 63% when injections were made on the twenty-second day and 50% when they were given on the forty-second day of gestation. Even light anesthetic doses produced maternal death, early aborting of young before term, and stillborn fetuses at term. How much of this mortality rate was directly attributable to poor housing conditions of stock and to disease rather than to the effects of the anesthetic is difficult to assess. Comparisons between placebo injections and Nembutal injections can be made only in animals of sixty-three days' gestation. All animals were equally exposed to the adverse conditions in the stockroom. No mothers injected on the sixty-third day died; still, the frequency of term stillborns in this category (66%) is high in contrast to 13% for placebo-injected animals.

Armitage[7] found that when rats that were full term at 21.3 days gestation were injected with certain of the barbiturates at 19.5 days gestation, maternal mortality rate was 38% and 39% of the offspring lived for no more than sixty hours. His dosage levels ranged from 30 to 40 mg. per kilogram. In his placebo group, no mothers died and only 15% of the offspring died shortly after birth. He did not find any of the neurologic signs in the rat that we report here for the guinea pig. Many workers[8–15] have pointed out how much more resistant the immature nervous system is to hypoxic stress than is the more mature type of nervous system. This observation may be sufficient to account for the differences between these two species of rodents in respect to the possible occurrence of neurologic deficits in the neonate.

So far as our particular study is concerned, we can only theorize as to whether a state of hypoxia, hypercapnia, or both existed in utero after drug administration. There is general agreement[16–19] that several of the barbiturates, Nembutal included, act chiefly to depress the respiratory center in the adult cat, rabbit, dog, and man. We[20] have found marked depression in respiratory rate and minute volume one-half hour after injecting the light dose, 28 mg. per kilogram, of Nembutal into the hearts of nonpregnant, adult female guinea pigs. The same dosage level given to normally born guinea pigs very shortly after birth produces similar results without residual neurologic deficit. But, a heavy dose, given to the normally born neonate, depresses respiration drastically and leads to the same neurologic symptomatology that we have described for our drugged cesarean deliveries. It would seem that the fetal center of the near-term fetus should not react much differently from that of the neonate.

If Nembutal, in fact, is a strong depressant of the respiratory center, why did we observe fetal respiratory-like efforts in utero? How is it that a normally quiescent fetal mechanism became activated, especially in the face of a depressant drug? Shortly after drug administration, we observed vasoconstriction and blanching of uterine vessels near placental sites in the majority of our water-bath deliveries. In these instances, fetal respiratory behavior always followed. It is possible, therefore, that such vasoconstrictor activity interfered with oxygen–carbon dioxide transport between mother and fetus in such a way as to either induce a state of hypoxic stress or cause a transient increase in fetal serum carbon dioxide. In either case, an activating mechanism would be brought to bear upon the fetal respiratory center. At the same time, vasoconstrictor activity could serve to limit the amount of drug getting across to the fetus per unit of time. The young delivered under these circumstances were always atonic and apneic.

Apparently, in lightly anesthetized litters, where vasoconstriction did not occur, drug concentration was not great enough to depress the fetal respiratory center nor were conditions present in utero which could activate the center. Fetal respiratory efforts were not seen in utero; the young were delivered with good muscular tone, and they breathed at once.

In the heavily anesthetized litters where vasoconstriction did not occur, it is possible that the drug passed the placental barrier in sufficient concentration to completely depress the fetal center. No fetal respiratory efforts were noted in utero, and, again, atonic and apneic young were delivered.

When our apneic neonates were resuscitated, the first respiratory responses were of the Hering-Breuer reflex type. Only much later did the center respond spontaneously. Guinea pigs rendered hypoxic in utero by clamping the uterine vessels are likewise delivered in apnea and respond in identical fashion to resuscitation with oxygen.

Unless one allows for the possibility of species differences, it is difficult to find ready support in the literature for the existence of a true hypoxic state during anesthesia with the barbiturates. On the basis of human data, Patrick and Faulconer[19] showed that, under the barbiturates, respiratory control was still predominantly a function of the respiratory center per se and that control was not given over to chemoreceptor mechanisms. Oxygen and carbon dioxide concentrations in arterial blood did not vary greatly from the normal values in the unanesthetized state.

Dripps and Dumke[18] and Moyer and Beecher[17] demonstrated that a true hypoxic state was reached in the dog and cat under deep narcosis with various of the barbiturates and that any respiration that occurred under these conditions was due primarily to chemoreceptor mechanisms responding to hypoxic stress.

Theoretically, at least, sodium pentobarbital should have no significant effect upon the cardiovascular system.[21] If this is entirely true, it makes it difficult to explain the constriction we observed in the uterine vessels of the majority of our litters. We can only report the fact that vasoconstriction and blanching often occurred in these vessels after drugs were administered to the mother.

Whether or not we are able to offer a completely satisfactory explanation for the occurrence of fetal intrauterine respiratory behavior—a phenomenon we had not expected to observe at all under Nembutal – in order to account for the spastic extremities and other signs of neurologic dysfunction encountered in our drugged neonates, even in those which breathed spontaneously at birth, it should be quite apparent that something was occurring in utero to interfere with neuronal metabolism. Even here, oxygen deprivation remains suspect since even hypnotic dosages of the anesthetic have been reported to lower cerebral oxygen consumption in the human being by 20%, independent of any change in cerebral blood flow.[21]

Heavily sedated mothers injected before delivery and allowed to bear their own young also gave birth to neonates exhibiting spastic paralysis. These young also must have breathed spontaneously at birth in order to survive. None of the intact, lightly anesthetized mothers bore spastic young. But the mortality rates at birth in both the intact and drugged groups were sufficiently great to allow for the possibility that the more severely damaged young never survived the birth process. Certainly it was true in the water-bath

experiments that no severely apneic fetus ever survived unless it was resuscitated by us.

While one hesitates to apply animal findings to the human sphere, there is a forceful implication in studies of this kind that misuse of the barbiturates to insure a painless delivery may inadvertently be a potent factor in the etiology of some of the manifestations associated with cerebral palsy.

SUMMARY

1. Guinea pigs, delivered near term as cesarean controls with no anesthesia other than procaine block of the maternal abdomen, breathed at once and displayed no signs of brain damage. In respect to birth weight, litter size, and survival, they were the equal of normally born young.

2. The litter mate controls delivered after either light or heavy sedation of the mother with pentobarbital sodium all suffered neural damage as reflected in: delayed righting; spastic limbs; reflex running movements; incoordinate gaits; head and trunk tremor; odd posture; loss of startle response; feeding difficulties, and piloerection. Most of these animals failed to breathe at birth and required resuscitation; others, breathing spontaneously, soon developed neurologic deficits. Intrauterine, fetal, respiratory-like efforts were frequently noted. In the majority of instances, shortly after drug administration, there was noticeable constriction and blanching of the uterine arteries.

3. In animals bearing their own young after administration of the anesthetic drug on either the twenty-second, forty-second, or sixty-third day of gestation, birth mortality was high. The surviving young showed only mild symptoms of brain damage which were reflected in awkward gait, hunched postures, and piloerection. They recovered within a week, and survival was comparable to young born of placebo-injected mothers.

4. Newborn young, heavily anesthetized shortly after birth, exhibited symptomatology as extreme as that observed in the cesarean deliveries under drug.

5. The neurologic manifestations of prenatally drugged animals closely resembled those seen in animals whose umbilical or uterine vessels had been occluded before delivery.

6. The role of the drug upon activation of the fetal respiratory center is discussed.

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Pneumotaxic localization, recording, stimulation, and section of basal brain structures in dyskinesia

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THE IMPORTANCE IN HUMAN BEHAVIOR of the nuclei at the base of the brain, and their proximity to the optic and the corticospinal tracts, make it imperative to localize lesions in this area as accurately as possible. Obviation of individual variations has been our aim during the past five years. Although results were satisfactory in most patients in whom the leukotome was used without a guide,[1] we have found the present method more reliable.[2,3]

METHOD

The procedure is done under local anesthesia. Roentgen rays are centered by fluoroscopy outside the patient's head. The head is fixed in a special frame and displaced mechanically – the central ray falling on the point to be studied on the ventriculogram. Within a radius of 1 cm., the distances measured on a grid are magnified less than 1 mm. A triple-lead needle-electrode is introduced parallel to the sagittal plane (Fig. 1). In final position, beta and theta rhythms are obtained from the middle contact lying at the site of the proposed lesion, while stimulation elicits motor or visual responses 8 mm. lower. Section is performed by quadrants with a blunt fine-wire leukotome, while movements and muscle tone are examined until pronounced hypotonia occurs.

Measurements were taken from either the center of the third ventricle or that of the foramen of Monro to the center of the lesion.

RESULTS

Of 40 patients, 35 have either become ambulatory, or if ambulatory, self-sufficient. Of these 35 patients, 12 show little or no symptoms of parkinsonism and have resumed skillful occupations.

Of 3 older patients, 2 had improved motor function but seemed to be less alert; 1 had had a previous injection in the globus region. The third patient had a sharp drop to 25% of normal prothrombin time on the day after operation and developed systemic bleeding, intracranial hematoma, and hemiparesis.

Although no immediate postoperative deaths occurred, 2 older patients died – 1 from pulmonary edema two weeks after operation, and the other from pulmonary emboli a month after operation. Serial brain sections from the edematous patient showed a well-circumscribed lesion of globus pallidus one and two.[3] No involvement of the corticospinal tract was found.

However, older patients should not automatically be denied operation. If older patients present no definite impairment of renal, respiratory, or cardiac function and understand and accept greater danger of complications, operation should be performed. In older patients, the lesion should be placed within the minor hemisphere where much less postoperative indifference and drowsiness are produced. Of 29 sections within the minor hemisphere, only 4 resulted in drowsiness, while 8 of 17 sections within the major hemisphere resulted in drowsiness, and 3 of the 8 had transitory akinetic mutism. Extreme drowsiness occurred in 1 of 8 patients with bilateral lesions. In

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older patients, the lesion should be well localized and not too large. Degree of ipsilateral improvement after unilateral lesions is sufficient to make such procedures worthwhile.

Operation should not be performed in younger patients if they are able to work.

At present, we do not doubt that rigidity and, eventually, bradykinesia and the fine tremor which accompanies these manifestations will be relieved if a lesion 12 mm. in diameter is centered 10 mm. below the foramen of Monro at 5 to 8 mm. behind that foramen and at 13 to 15 mm. from the midline.

Large amplitude tremor with hypotonia requires a more posterior lesion—usually 10 mm. behind the foramen of Monro. Either form of tremor may reappear under emotional tension.

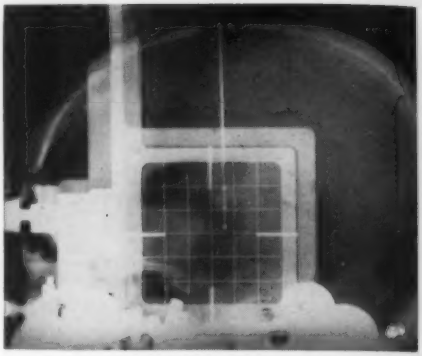

FIG. 1. Lateral view showing pneumotaxic guide fixed on the head of a patient with triple-lead depth electrode in place for recording and stimulation

INCIDENTAL FINDINGS

Since prothrombin time was found to be abnormally low postoperatively in 1 patient, vitamin K is always administered postoperatively.[3] In 10 patients, values of prothrombin time were determined at frequent intervals before giving vitamin K. Values fell from normal (between 92 and 100%) to levels between 52 and 76% in six to twelve hours postoperatively and from 25 to 75% in twelve to eighteen hours. Of 6 patients who were studied for one to three days, 4 had values between 25 and 40%. In 2, readings were 55 and 72%. Prothrombin time was promptly restored to normal in all patients by administration of vitamin K. After a week, prothrombin time remained normal without further administration of the vitamin. Prothrombin time was still above 85% when determined four months postoperatively. The mechanism involved is being investigated further, but, meanwhile, use of vitamin K after operation is strongly recommended.

Examination of the pneumograms in 52 patients suggested a difference between the pattern of cerebral damage in the postencephalitic and the senile forms of the disease. Patients were divided into 2 groups: patients less than 50 years old and patients 50 or older.

Almost all younger patients are assumed to have postencephalitic parkinsonism—parkinsonism not related to cerebral vascular changes. Of 26 patients in the younger group, 24 had large ventricles. In 16 of these, ventricular dilation alone was observed (Fig. 2). Enlargement of cortical sulci and ventricular dilation were found in 8, and 2 had dilation of cortical sulci alone.

In the older group, 15 of 26 patients had enlargement of cortical sulci with normal ventricles (Fig. 3); 8 had some ventricular enlargement and enlarged cortical sulci; 3 had ventricular dilation alone.

The senile or arteriosclerotic form of the disease is very similar to cerebral arteriosclerosis without Parkinson's disease and may be due to circulatory changes, being evident at cortex level.

The pathology revealed by the pneumograms agrees with the high percentage of electroencephalographic abnormalities found in preoperative scalp records. Of these, 80% suggested diffuse cerebral disease. At the site of the projected lesion, depth electroencephalography showed typical ganglion cell activity consisting mostly of beta and some alpha and theta rhythms. In 4 patients in whom lowest contact had yielded visual responses on stimulation, opening and closing of the eyes always elicited a response—a diphasic wave, with a short positive and long negative wave.

Most responses to stimulation were either localized motor responses of the rolandic type or visual phenomena reported by the patients as white flashes of light in the contralateral visual field.

In 2 patients using the same parameters (2

FIG. 2. Ventriculoencephalogram in a patient with postencephalitic parkinsonism

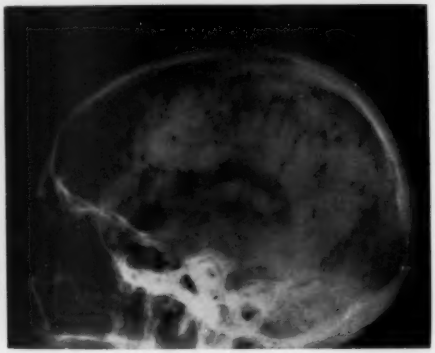

FIG. 3. Pneumoencephalogram in a patient with senile parkinsonism

m.sec., 60 cps., 1 to 4 volts), tremor was definitely initiated or increased by stimulation.

Sustained tremor at rest was observed in 6 of 14 monkeys in which lesions were placed in the ventromedial part of the tegmentum at the level of the third nerve; in some, tremor remained unaltered until sacrifice of the animals six months later.

CHOREOATHETOSIS

After treatment, relief and, in some cases, return to a fairly normal life are possible in patients with choreoathetosis. However, no improvement occurs unless the lesion is carried back far enough to section the motor fibers and produce nearly complete paralysis. With this technic, the degree of paralysis can be assessed as the lesion is being carried out, since only enough anesthesia is given to prevent large amplitude movements during the procedure. In 2 patients treated by this method, the lesions were centered 13 mm. behind the foramen of Monro. These patients were anarthric for a few weeks after the second lesion on the side of the major hemisphere – a fact which had not been observed after sections in previous patients with choreoathetosis. Eventually, speech was easier to understand than before operation. While dystonia musculorum deformans is relieved by lesions of the globus pallidus, choreoathetosis is not improved unless the lesion involves the motor pathways.

DISCUSSION

In order to take direct measurements on a grid outside the patient's head without using teleradiography, roentgen rays of a standard craniograph are centered with a fluoroscope and mobile head holder. The small degree of magnification – less than 1 mm. – about this central point can be determined by measuring on a roentgen film the distance between the three leads of the needle-electrode. While recording verifies proper positioning within the globus, stimulation detects the proximity of motor or visual fibers. Leukotomy may not be a sophisticated way of destroying brain tissue; however, a fine-wire, blunt leukotome creates a well-circumscribed, visible lesion and is quite safe when properly used. The leukotome also appears to brush away the optic tract in proximity to which a proper lesion must be placed.

Almost all lesions are about 10 mm. below the center of, and 5 to 8 mm. behind, the foramen of Monro, if rigidity is the presenting symptom, and 8 to 10 mm. behind the foramen when tremor is the main symptom. Variations in the lateral distance from the midline are less important and may extend from 13 to 17 mm., although most of them are 13 to 15 mm. from the midline. These figures are so constant that frequently a significant effect is produced when a brain slice only 2 or 3 mm. thick has been destroyed. Even then, the lesion is usually completed by successive sections to insure permanent results. The area destroyed should not be larger than necessary. The transitory indifference and drowsiness, more apparent in sclerotic patients, the lobotomy-like effect obtained in a few patients when a contralateral lesion

was done shortly after the first section, and the mental sluggishness and diminution of creative power observed in an artist in whom section was done after an injection had been performed elsewhere point to the importance of these structures and to the necessity of minimizing lesions within them. Compensatory mechanisms are usually excellent within these highly integrated structures, but one should not anticipate too much in older or severely handicapped individuals. Apparent improvement in mental alertness and mental agility frequently following these operations may be caused by greater motor activity and an increased facility of expression. Further improvement of motor function should not be sought at the risk of altering or diminishing a patient's mental activity. Since lesions of the globus are so effective, we have not used thalamic lesions advocated by Riechert[4] and Cooper.[5]

The few patients operated on three to five years ago have maintained their improvement.

We are convinced that involvement of the motor fibers of the corticospinal tract can no longer be considered important in results obtained because of [1] absence of any detectable lesion of the corticospinal tract on serial sections of 2 pathologic specimens, [2] beneficial rather than detrimental effect on motor power of the lesions, [3] lack of any sustained pyramidal tract signs in any patient, [4] the satisfactory result obtained in patients in whom lesion was more anterolateral and farther from the internal capsule, and [5] the sharp contrast between the effect of lesions of the globus and those of capsular lesions used in choreoathetosis.

A corollary to this type of operation is the occasional transitory difficulty in initiating movements of the contralateral hand after operation; wet, this difficulty seems different from neglect seen in parietal lobe lesions.[6] When asked to move his hand, the patient is unable to do so immediately. Hand movements, when performed, are well coordinated and agile. This phenomenon may be related to transitory akinetic mutism seen in 3 patients after section in a major hemisphere.

SUMMARY

With the method described, well localized, visible, circumscribed lesions are produced and controlled by radiology, depth electroencephalogram, stimulation, and neurologic examination during operation. Of 40 patients 35 were benefited by such lesions.

In a few patients studied specifically, prothrombin time was found to drop abruptly immediately after section within the globus but was promptly restored to normal by use of vitamin K.

In the pneumograms of 52 patients, ventricular dilation was found to be typical of postencephalitic parkinsonism, while cortical atrophy was seen almost exclusively in the senile or arteriosclerotic form of the disease.

Cerebral dysrhythmia was seen in 80% of preoperative electroencephalograms.

Depth recording within the globus showed typical ganglion cell activity.

In most patients, stimulation elicited motor or visual responses immediately below the site of the proposed lesion. In 2 patients, tremor was initiated by stimulation within the globus pallidus.

In patients with Parkinson's disease, tremor and rigidity were improved by lesions of the globus pallidus without involvement of the voluntary motor fibers of the internal capsule. In patients with choreoathetosis, fibers had to be sectioned to abolish abnormal movements.

To prevent complications, lesions within the basal ganglia should be localized accurately and unnecessarily large lesions avoided.

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Effects of blood *p*H and carbon dioxide on cerebral electrical activity

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CHANGES in the partial pressure of carbon dioxide in the blood and tissues are reflected by alterations of function of the central nervous system. A healthy person experiences lightheadedness and confusion when the partial pressure of carbon dioxide (CO_2) is lowered by hyperventilation. Hypocapnia precipitates petit mal regularly and occasionally induces focal cortical seizures. Raising the partial pressure of arterial carbon dioxide causes somnolence and movement disorders.[1] Coma may result when the arterial partial pressure of carbon dioxide exceeds 100 mm. Hg.[2] Prominent electroencephalographic changes accompany both lowered and elevated arterial carbon dioxide concentrations.[3]

Carbon dioxide exists in body fluids both as a dissolved gas and as dissociated carbonic acid. Because of the acid properties of carbon dioxide in solution, the hydrogen ion content of body fluids rises or falls when the carbon dioxide tension is raised or lowered. The question arises whether the change in molecular carbon dioxide or the concomitant creation of arterial acidosis or alkalosis is more responsible for influencing neural activity. Lubin and Price[4] concluded that the effect of carbon dioxide on neural function was specific. The alternate view—that carbon dioxide effects are merely those of changing the acid-base balance—recently appeared to gain support when a patient with carbon dioxide narcosis improved after a bicarbonate dialysis that raised the serum *p*H.[5] The present experiments were designed to provide a more controlled evaluation of the mode of action of carbon dioxide in the nervous system. Cerebral electrical activity was recorded in cats, and the partial pressure of arterial carbon dioxide was manipulated independenly from changes in the arterial *p*H.

METHOD

Apnea was induced in 28 unpremedicated cats weighing approximately 3 kg. each with single intravenous injections of succinylcholine, 800 μg. per kilogram. The animals were immediately intubated with a cuffed endotracheal tube and ventilated with room air by means of an intermittent positive pressure respirator. D-tubocurarine, 2 mg. per kilogram, was injected intravenously to maintain complete muscle paralysis for a prolonged period. The alveolar carbon dioxide tension ($PACO_2$) was monitored continuously with a Liston-Becker infrared carbon dioxide analyzer, the expired air sample being drawn from a catheter placed deep in the trachea in the vicinity of the carina. The output from the carbon dioxide analyzer was recorded by an Esterline-Angus inkwriter. Arterial blood samples were obtained at intervals through an indwelling femoral artery catheter and analyzed directly for oxygen and carbon dioxide content by the Van Slyke manometric technic. Arterial blood *p*H was determined on the same fresh samples using a Cambridge model R *p*H meter outfitted with a Coleman microchamber electrode. The arterial carbon dioxide tension ($PaCO_2$) was calculated from the Singer-Hastings nomogram. Correlation between the analyzer measurements of alveolar carbon dioxide tension and simultaneously measured arterial carbon dioxide tension was within 1 to 3 mm. Hg, the arterial value being higher. Experiments in which the arterial oxygen saturation fell below 85% were discarded. The

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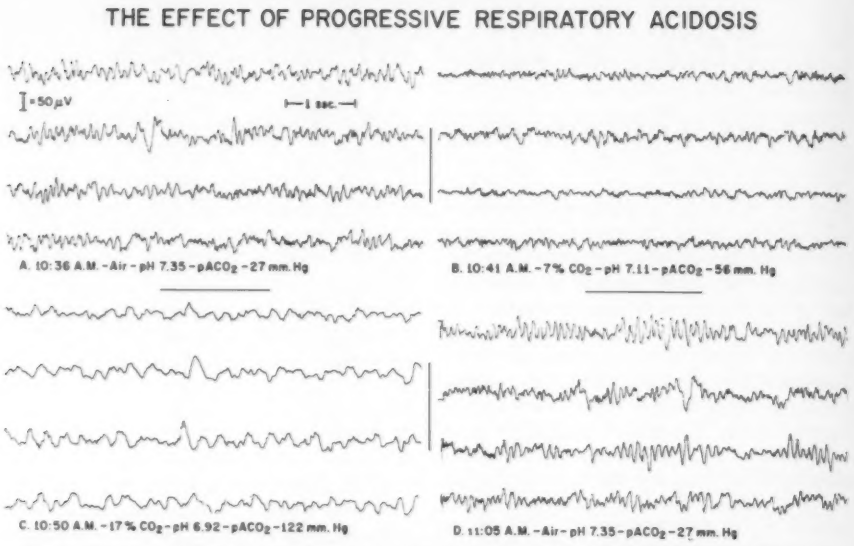
THE EFFECT OF PROGRESSIVE RESPIRATORY ACIDOSIS
I=50μV
1 sec.
A. 10:36 A.M. - Air - pH 7.35 - pACO2 - 27 mm. Hg
B. 10:41 A.M. - 7% CO2 - pH 7.11 - pACO2 - 56 mm. Hg
C. 10:50 A.M. - 17% CO2 - pH 6.92 - pACO2 - 122 mm. Hg
D. 11:05 A.M. - Air - pH 7.35 - pACO2 - 27 mm. Hg

Fig. 1. Electroencephalographic recordings in a cat exposed for five minutes to inhalation of 7 and 17% carbon dioxide (CO_2), respectively, with ventilation kept constant. In this and subsequent figures, the electrode placement is as described under Method.

electroencephalogram was recorded from phonograph needles driven through the calvarium and used as electrodes. Bipolar recordings were taken with the electrodes placed as follows: channel 1, right anterior–right central; channel 2, right central–right occipital; channel 3, left frontal–left central; and channel 4, left central–left occipital.

The control respiratory minute volume was adjusted for each animal to maintain an arterial *p*H range of 7.35 to 7.42. The recorded alveolar carbon dioxide tension at these levels varied between 25 and 37 mm. Hg. After a control period of recording, the effects of breathing mixtures of carbon dioxide in air and hyperventilation on the electroencephalogram were first examined to determine the effects of hypercapnic acidosis and alkalosis. Then, widely spaced injections of sodium carbonate (Na_2CO_3) and sodium bicarbonate ($NaHCO_3$) were given intravenously to manipulate the arterial *p*H and carbon dioxide tension independently. Both compounds produced alkalosis, but sodium carbonate briefly lowered while sodium bicarbonate briefly raised arterial carbon dioxide tension. Finally, hydrochloric acid (HCl) was injected intravenously to determine the electroencephalographic effects of a marked increase in hydrion concentration unaccompanied by sustained alterations in carbon dioxide tension. In general, the effects of sodium carbonate, sodium bicarbonate, and hydrochloric acid, respectively, were determined on separate animals on separate days. The ventilation was kept constant throughout the experiments except when hyperventilation was produced intentionally.

RESULTS

Effect of hypercapnic (respiratory) acidosis. Respiratory acidosis was induced in 7 cats breathing 7 and 17% carbon dioxide. Figure 1 illustrates a typical experiment.

Moderate lowering of arterial blood *p*H from 7.35 to 7.11 and elevation of the alveolar carbon dioxide tension from 27 to 56 mm. Hg changed the electroencephalogram from a control pattern of 8 to 12 cps with an amplitude of about 50 μv. to a faster rhythm with a lower voltage. The arterial *p*H was further lowered to 6.92 and the alveolar carbon dioxide tension increased to 122 mm. Hg by 17% carbon dioxide. The electroencephalogram slowed to 2 to 3 cps with moderately high amplitude

waves. When room air was breathed again, the *p*H and alveolar carbon dioxide tension returned to the control levels and the electroencephalogram resumed its previous pattern.

The Effect of hypocapnic (respiratory) alkalosis. Respiratory alkalosis was produced in 6 cats by doubling the tidal volume (Fig. 2). With hyperventilation, the arterial *p*H rose from 7.42 to 7.58 and the alveolar carbon dioxide tension fell from 27 to 9 mm. Hg. The electroencephalogram slowed to 4 to 5 cps, and very high voltage waves appeared (Fig. 2B). When hyperventilation ceased, the *p*H and alveolar carbon dioxide tension returned to control values and the electroencephalogram resumed a normal pattern.

Effect of sodium carbonate. Injection of 10 mEq. of 1N sodium carbonate was done intravenously in 3 animals during eupnea for ten seconds (Fig. 3A, B, and C). The *p*H rose from 7.35 to 7.59, and the alveolar carbon dioxide tension fell transiently from 26 to 14 mm. Hg. The electroencephalogram assumed a low-frequency, high-voltage pattern similar to that seen when the alveolar carbon dioxide

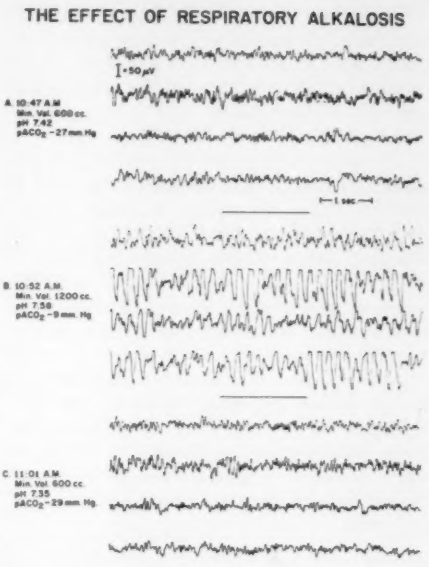

Fig. 2. Electroencephalographic recordings in a cat exposed to five minutes of hyperventilation

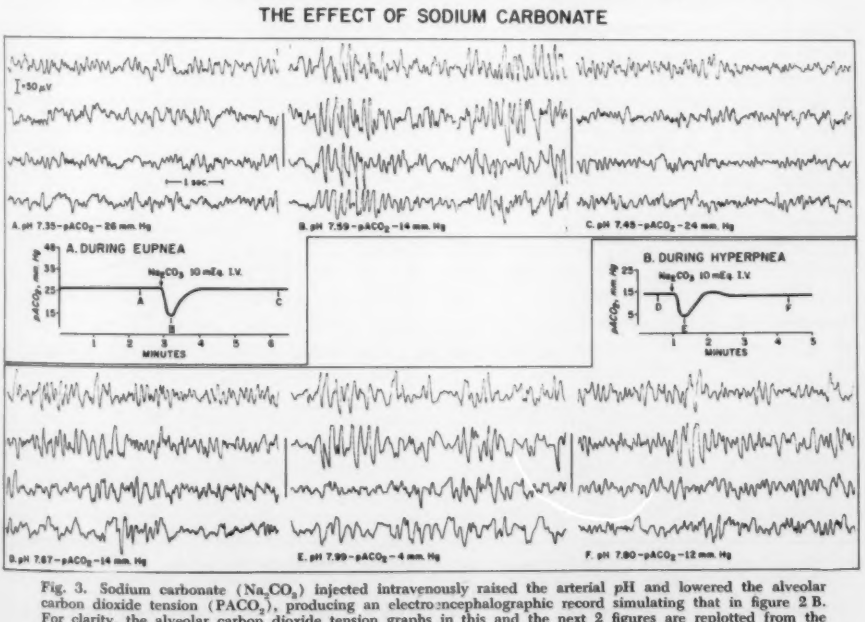
THE EFFECT OF SODIUM CARBONATE
I=50 μV
1 sec
A. pH 7.35 – pACO2 – 26 mm. Hg
B. pH 7.59 – pACO2 – 14 mm. Hg
C. pH 7.45 – pACO2 – 24 mm. Hg
A. DURING EUPNEA
Na2CO3 10 mEq. I.V.
pACO2, mm Hg
MINUTES
B. DURING HYPERPNEA
Na2CO3 10 mEq. I.V.
pACO2, mm Hg
MINUTES
D. pH 7.67 – pACO2 – 14 mm. Hg
E. pH 7.99 – pACO2 – 4 mm. Hg
F. pH 7.80 – pACO2 – 12 mm. Hg

Fig. 3. Sodium carbonate (Na_2CO_3) injected intravenously raised the arterial *p*H and lowered the alveolar carbon dioxide tension ($PACO_2$), producing an electroencephalographic record simulating that in figure 2 B. For clarity, the alveolar carbon dioxide tension graphs in this and the next 2 figures are replotted from the original Esterline-Angus recordings. The letters along the alveolar carbon dioxide tension graphs indicate the points at which the representative blood samples and tracings were taken.

tension was reduced by hyperventilation. The electroencephalogram resumed its control pattern when the alveolar carbon dioxide tension returned to normal, although the arterial blood *p*H was 0.1 unit higher than during the control period.

The above experiment was repeated on passively hyperventilated animals (Fig. 3D, E, and F). When the sodium carbonate was injected, the *p*H rose from 7.67 to 7.99 and the alveolar carbon dioxide tension fell from 14 to 4 mm. Hg. The electroencephalogram developed more marked slowing and showed an exaggerated form of the hyperventilation record. The opposite was observed when animals inhaled mixtures of 17% carbon dioxide in air before sodium carbonate injection. The slow, rolling, delta pattern of the electroencephalogram produced by breathing 17% carbon dioxide returned to normal during sodium carbonate-induced alveolar carbon dioxide tension reduction.

Effect of sodium bicarbonate. Intravenous injection of 10 mEq. of 1N sodium bicarbonate was done in 3 animals for ten seconds. The *p*H rose from 7.36 to 7.62, and the alveolar carbon dioxide tension increased from 36 to 44 mm. Hg. Instead of the 4 to 5 cps high-voltage waves seen with sodium carbonate injection, only moderate slowing and occasional delta waves were produced. The record (Fig. 4A, B, and C) resembled the electroencephalogram seen during 7% carbon dioxide inhalation. The effect of sodium bicarbonate was demonstrated more dramatically by previously hyperventilating animals enough to raise the *p*H to 7.91 and lower the carbon dioxide tension to 8 mm. Hg. Hyperventilation markedly slowed and increased voltage of the electroencephalogram. Rapid injection of sodium bicarbonate then produced a transient return of the electroencephalogram to normal (Fig. 4D, E, and F). This occurred while the carbon dioxide tension was raised to 17

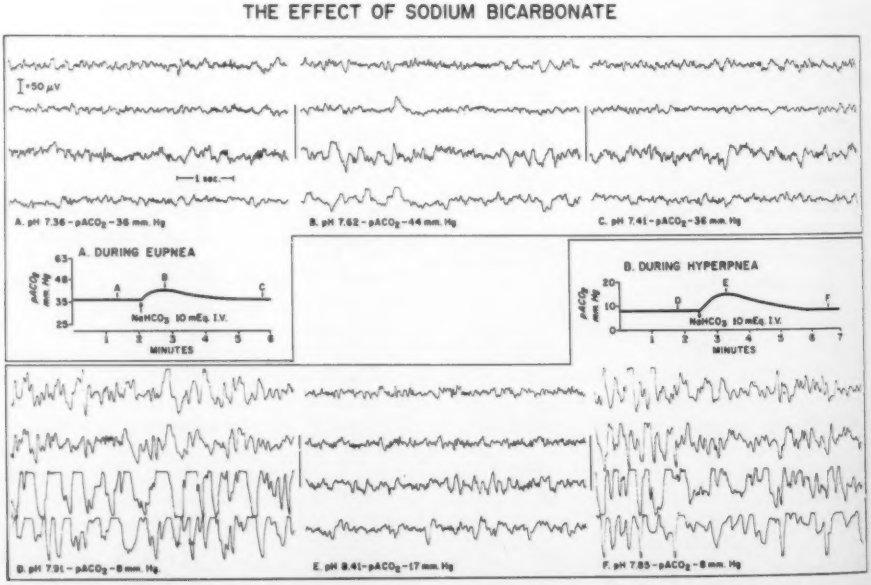
THE EFFECT OF SODIUM BICARBONATE
I=50 μV
1 sec.
A. pH 7.36 - pACO2 - 36 mm. Hg
B. pH 7.62 - pACO2 - 44 mm. Hg
C. pH 7.41 - pACO2 - 36 mm. Hg
A. DURING EUPNEA
pACO2 mm Hg
NaHCO3 10 mEq. I.V.
MINUTES
B. DURING HYPERPNEA
pACO2 mm Hg
NaHCO3 10 mEq. I.V.
MINUTES
D. pH 7.91 - pACO2 - 8 mm. Hg.
E. pH 8.41 - pACO2 - 17 mm. Hg
F. pH 7.85 - pACO2 - 8 mm. Hg

Fig. 4. Sodium bicarbonate ($NaHCO_3$) injected intravenously raised the arterial pH but also raised the alveolar carbon dioxide tension. During the period of alveolar carbon dioxide tension elevation, the electroencephalogram taken during eupnea became slower and resembled the effects of 7% carbon dioxide (Fig. 1B). When the animal was hyperventilated before infusing sodium bicarbonate, the electroencephalogram returned toward normal during the time that alveolar carbon dioxide tension was raised. This latter change occurred despite an arterial pH of 8.41.

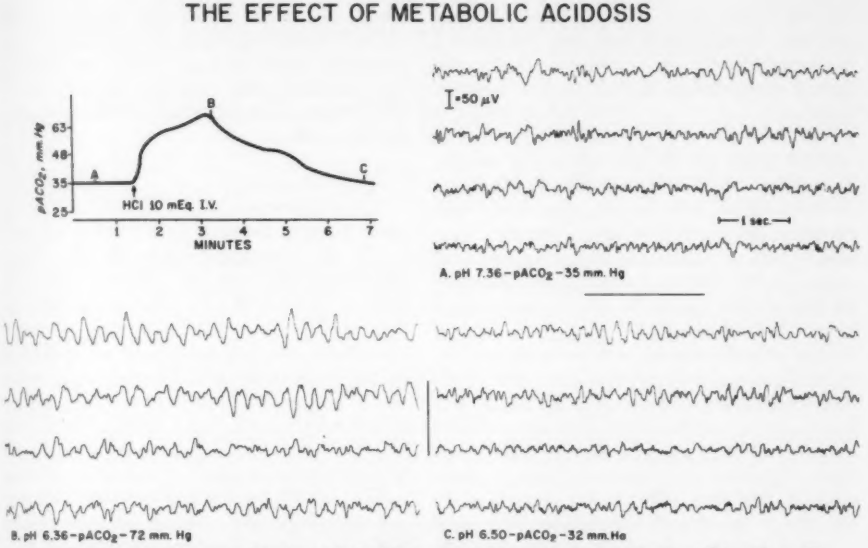

Fig. 5. Although intravenous injection of hydrochloric acid (HCl) produced a profound acidosis with a pH of 6.5, the electroencephalogram slowed significantly only while the alveolar CO_2 tension was elevated.

mm. Hg, despite a simultaneous rise in the arterial *p*H to 8.41. The electroencephalographic changes presented a strong contrast to the pattern produced by sodium carbonate. This contrast in action was demonstrated further by injecting sodium bicarbonate into animals first made acidotic by 17% carbon dioxide inhalation; no significant change was observed in the electroencephalogram during bicarbonate injection.

Effect of metabolic acidosis. In 3 animals, 10 mEq. of 1N hydrochloric acid was injected intravenously for ten seconds (Fig. 5). A sustained acidosis, with a *p*H of 6.36 and a transient rise in alveolar carbon dioxide tension to 72 mm. Hg, resulted. The electroencephalogram slowed and resembled the effect of breathing carbon dioxide during the period of alveolar carbon dioxide tension elevation (Fig. 5B). When the alveolar carbon dioxide tension returned to 32 mm. Hg, approximately the preinjection level, the electroencephalogram resumed its control pattern, despite the severely acidotic blood *p*H of 6.5 (Fig. 5C).

DISCUSSION

In these experiments, rapid alterations of the carbon dioxide tension in the arterial blood caused characteristic and recognizable changes in the electroencephalogram. When the alveolar carbon dioxide tension and arterial blood *p*H were manipulated independently, the change in the electroencephalogram followed the direction of change in carbon dioxide and bore no relationship to the arterial blood *p*H. Thus, sodium carbonate injection, which raised the blood *p*H and transiently lowered the alveolar carbon dioxide tension, produced an electroencephalogram characteristic of hyperventilation. Sodium bicarbonate, which also raised the blood *p*H but elevated the alveolar carbon dioxide tension, produced an electroencephalogram similar to that caused by breathing carbon dioxide. Metabolic acidosis, induced by injection of hydrochloric acid, affected the electroencephalogram only during the period when alveolar carbon dioxide tension was elevated.

Correlates to the differential effects of sodium carbonate and bicarbonate on the electroencephalogram have been described in studies on respiration. Hesser[6] found that intravenous sodium carbonate produced a fall in blood carbon dioxide tension and a transient decrease in respiration, while intravenous sodium bicarbonate produced a rise in carbon

dioxide tension and a transient increase in respiration. Hydrochloric acid also produced a transient increase in respiration during the period when carbon dioxide tension was elevated.

The fact that abruptly induced changes in arterial blood *p*H do not affect the electroencephalogram does not imply that changes in intracellular *p*H do not alter nerve cell function and cortical electrical activity. Carbon dioxide in solution is unique in that it is only partially ionized and is highly diffusible.[7] In vivo recordings of the *p*H of the cerebral cortex have revealed that changes in arterial carbon dioxide tension are accompanied by rapid changes in cortical *p*H.[8] The facility with which carbon dioxide changes intracellular *p*H was shown by Jacobs,[9] who demonstrated that tadpoles could not survive in solutions of carbonic acid but could live in solutions of other acids at the same *p*H. In experiments with the flower *symphytum peregrinum*, the cells of which change color when the internal *p*H changes, Jacobs[10] found that solutions of carbon dioxide caused a prompt color change, while solutions of HCl at the same *p*H did not. Sea urchin eggs prepared with a color indicator reacted in a similar fashion. Winterstein[11] demonstrated the ability of carbon dioxide to diffuse across semipermeable, nonliving membranes that were impermeable to other acids.

It cannot be deduced at present whether the effect of carbon dioxide on the electroencephalogram results from a change in intracellular *p*H or more specific action of the carbon dioxide molecule. Acute changes in blood acidity or alkalinity had no effect on the electroencephalogram unless the *p*H change was accompanied by an appropriate alteration in the alveolar carbon dioxide tension. Hence, correction of blood acidosis without reduction of the carbon dioxide tension is unlikely to improve the neurologic abnormalities of carbon dioxide narcosis.

SUMMARY

Rapid alterations of the alveolar carbon dioxide tension produce characteristic changes in the electroencephalograms of cats. When the arterial *p*H and the alveolar carbon dioxide tension ($PACO_2$) are manipulated independently, the changes in the electroencephalogram are characteristic for the induced partial pressure of carbon dioxide and are not related to the arterial blood *p*H. Both sodium carbonate (Na_2CO_3) and sodium bicarbonate ($NaHCO_3$) markedly increase arterial *p*H. Sodium carbonate infusion lowers the alveolar carbon dioxide tension and produces the electroencephalographic changes of hyperventilation. In contrast, sodium bicarbonate transiently raises the alveolar carbon dioxide tension and, during the elevation, the electroencephalogram resembles the tracing produced by breathing carbon dioxide. Intravenous hydrochloric acid (HCl) induces both severe arterial blood acidosis and a transient rise in carbon dioxide tension. The electroencephalogram is altered only during the time when the alveolar carbon dioxide tension is increased.

Acute changes in arterial blood *p*H affect the electroencephalogram only when the *p*H change is accompanied by an alteration in blood carbon dioxide tension. Carbon dioxide possesses unique properties that influence nerve cell function and cerebral electrical activity.

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Biothesiometry in the diagnosis of lumbar disk protrusion

Ib Steiness, M.D.

PATIENTS receiving neurosurgical treatment for protrusion of lumbar intervertebral disks usually have the lumbago-sciatica syndrome. Of 580 patients in whom operation was performed, 562 had this syndrome.[1,2]

The lumbago-sciatica syndrome may be subdivided into various syndromes due to compression of third, fourth, or fifth lumbar or first sacral root caused by protrusion of the second, third, fourth, or fifth lumbar disk. Solitary protrusion of the fourth or fifth disk is the most frequent lesion—constituting 95.6% of the disk protrusions seen in this department.[3]

Malmros[2] found pronounced monoradicular syndrome in 58 of 96 consecutive patients with the lumbago-sciatica syndrome on whom operation was performed for solitary disk protrusion. In only 48 was diagnosis in agreement with findings at operation. In 38, only a diagnosis of protrusion of the fourth or fifth disk could be made.

The purpose of this investigation was to find whether diagnosis of disk protrusion level could be made by quantitatively determining vibratory perception with a biothesiometer.

Zervopoulos[4,5] studied the vibratory perception on the malleoli in patients with protrusion of lumbar disks. He found this method was reliable in ascertaining disk protrusion level. Vibratory sensibility was reduced on the medial malleolus in protrusion of the fourth lumbar disk and on the lateral malleolus in protrusion of the fifth lumbar disk. In lateral protrusion, diminution in sensibility was homolateral; in central protrusion, bilateral. Each of 60 patients showed agreement between alteration in vibration sense and findings at operation. Zervopoulos' examination technic is not stated.

METHOD

A biothesiometer manufactured by Bio-Medical Instrument Company, Chagrin Falls, Ohio, was used to study vibratory perception. The biothesiometer and examination technic have been described.[6] Amplitude is expressed in volt units; maximum value is 50 volts.

SITES OF MEASUREMENT

Bilateral measurements were performed on digital pulps of the great and little toes and on the medial and lateral malleoli.

Measurements were also performed on the patella, the medial and lateral epicondyles of the femur, and, at first, on the calf. However, in agreement with the results obtained by Iversen[7] and others, results found on these sites were often doubtful.

CASE MATERIAL

In the series were 15 men and 4 women who received initial surgical treatment for unilateral lumbago-sciatica syndrome between January and September 1957 (Table 3). Previously, the patients had not had diseases which are known or suspected to affect vibratory perception. At examination, all had normal neurologic conditions on the unaffected side.

RESULTS

Operation revealed solitary protrusion of the third lumbar disk in 1; of the fourth in 10; and of the fifth in 7.

Fixation of the first sacral root, without protrusion, occurred in 1 patient, while 1 had fixation of the first sacral root with solitary protrusion of the fourth lumbar disk. Vibratory perception was not significantly diminished on the lateral malleolus on the affected side, as compared with the opposite side.

Threshold could be determined in all but 1 patient in whom maximum 50-volt amplitude

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of the biothesiometer could not be felt on the little toe on the affected side.

On one or more sites of measurement on the affected side, threshold in 7 patients was found to be significantly increased compared with the opposite side (Table 3). These 7 did not differ from the remaining patients regarding localization of protrusion, duration of symptoms, course of disease, other sensory or motor disturbances, reflex anomalies, or Lasègue's sign. Of the remaining 11 patients, 6 had sensory disturbances, 5 had motor disturbances, and 6 had hypo- or areflexia on affected side without accompanying changes in vibratory perception.

Only in 2 patients was a significant homolateral difference observed in the perception on medial and lateral malleoli on the affected side. In both patients, threshold was higher on lateral malleolus than on medial malleolus. Differences were 11 and 10 volt units, respectively. Patient 19613 had lateral protrusion of the fourth lumbar disk. Patient 20014 had lateral protrusion of the fifth lumbar disk. Therefore, results of the present study are at variance with those of Zervopoulos.

Difference in vibratory perception threshold between the two sides does not aid diagnosis of protrusion level (Table 3).

TABLE 1

Age	*15*	*25*	*35*	*45*	*55*
Great toe					
Mean	8.5	10.0	11.8	14.1	17.0
Maximum	15.6	18.9	23.1	28.3	34.9
Medial malleolus					
Mean	8.7	9.9	11.5	13.3	15.6
Maximum	14.6	17.2	20.3	24.1	28.8

Calculated means and upper limits of normal variations at the 97.5% maximum level expressed in volt units for 100 healthy subjects. Sex difference has been disregarded.

Upper limit of normal variation is approximate, 6 values for the great toe and 4 for the medial malleolus were above the upper limit as compared with the expected 2.5.

TABLE 2

	Great toe	*Little toe*	*Medial malleolus*	*Lateral malleolus*
Threshold	13	12.4	9.8	9.8

Average of vibratory perception threshold in volt units on the right foot in 5 healthy men and 5 healthy women 19 to 27 years old.

DISCUSSION

Using the biothesiometer, vibratory perception on the digital pulp of the great toe and

TABLE 3

Patient	*Sex*	*Age*	*Side*	*Level and position*	*Lasegue's sign*	*Sensory disturbance*	*Areflexia*	*Motor disturbance*	*Great toe* R	*Great toe* L	*Little toe* R	*Little toe* L	*Medial malleolus* R	*Medial malleolus* L	*Lateral malleolus* R	*Lateral malleolus* L
19450	F	39	R	4 l	O	+	P	+	*33* »	12	*32* >	*22*	*30* »	10	*33* »	9
19613	M	55	L	4 l	+	+	A	O	19 «	*47*	20 «	32	21	27	24 «	*38*
19904	M	52	L	4 m	+	O	O	+	*43*	*50*	*41*	*48*	19 «	*31*	19 <	*30*
20343	M	33	L	4 m	+	+	O	+	18 <	*28*	19	20	13	16	11	15
19582	M	55	L	4 l	+	+	A	+	27 <	*37*	29 <	*38*	24 «	*37*	27 «	*43*
19660	M	43	R	5 l	O	O	A	O	*38* »	22	20	20	19	18	13	14
20014	M	55	R	5 l	O	+	(A)	+	*50* »	*39*	— »	28	*39*	*37*	*49* »	*35*
17148	M	39	R	4 m	+	O	(A) (P)	O	12	15	10	12	14	13	16	14
19226	F	45	R	5 l	+	+	A	O	10	10	12	11	11	11	13	12
19293	M	31	L	5 l	+	+	(A)	+	11	13	10	10	9	11	11	11
19636	F	22	R	5 ?	O	O	O	+	*21*	13	14	14	12	11	14	13
19654	M	55	R	4 l	O	O	O	O	16	17	23	18	13	13	11	16
19774	M	23	R	4 l	+	O	O	O	12	12	15	16	11	13	12	14
20128	M	49	L	3 m	O	+	P	+	27	*32*	*33*	*32*	*28*	*28*	24	25
20153	M	43	L	5 l	+	O	PA	O	17	15	16	16	15	15	18	15
20199	F	39	L	5 m	O	+	(A)	+	*27*	*28*	21	20	18	17	17	18
20229	M	44	R	4 m	O	+	O	+	24	22	20	22	13	14	13	14
20336	M	23	L	4 l	++	+	O	O	16	15	11	13	11	11	10	10
15536	M	44	L	O	O	+	A	+	19	18	18	17	14	14	14	20

Level and position: median (m) or lateral (l) intraspinal protrusion. Lasegue's sign: ++, positive below 30°; +, positive between 30° and 50°; values above 50° may be due not only to tension of the nerve root but also to movements in the lumbar column[1] and are omitted. Areflexia: A and P indicate absence of Achilles-tendon reflex and patellar reflex; (A) and (P) indicate these reflexes were diminished as compared with opposite leg.

Last four columns show vibratory perception thresholds; italicized figures indicate values higher than calculated upper limit of normal variation (table 1). A single or double sign of inequality indicates a difference between the two sides at the 95.5% and the 99% level; minus signifies that vibrations could not be felt at 50-volt amplitude.

Elective atrophy was found in patients 19450 and 19904.

Patient 19582 had an attack of severe sciatic pain 20 years before operation. Operation revealed not only protrusion of fourth lumbar disk, but also severe fixation of first sacral root.

Patient 15536 had fixation of the first sacral root—without protrusion.

on the medial malleolus was studied in 100 healthy subjects.[6]

Threshold depends on age and sex; individual variations are wide. Table 1 shows the calculated means and the upper limits of normal variation at the 97.5% level. Sex difference has been disregarded.

In contrast to large, interindividual threshold variations, no statistically significant difference exists between right and left sides. Intraindividual dispersions are much smaller. The limits of significance for differences between the right and left legs on the digital pulps of the great toes were $\geqq$ 9 volt units at the 95.5% level and $\geqq$ 11 volt units at the 99% level. Corresponding values on the medial malleoli were $\geqq$ 10 and $\geqq$ 12 volt units, respectively.

Because vibratory perception is almost the same on great and little toes and on medial and lateral malleoli[7] (table 2), the same limits of significance were used in the analysis for toes and malleoli.

SUMMARY

Biothesiometric examination does not determine disk protrusion level.

Using a biothesiometer on the feet of 19 patients with unilateral lumbago-sciatica syndrome, vibratory perception threshold was determined.

Operation revealed solitary lumbar disk protrusion in 18. Compared with the unaffected side, vibratory perception threshold in 7 was significantly increased on one or more sites of measurement on the affected side.

Patients who had differences in vibratory perception threshold between the two sides did not differ in other respects from remaining patients of the series.

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Neurology at the crossroads

Sir Francis Walshe

THE PROBLEM of the future of neurology deeply concerns all members of this international congress, and this conference, I hope, not only will allow the ventilation of the fears that some of us feel as to present trends but also will provide us with some general ideas and guidance as to how neurology may best meet the urgent and increasing demands made upon it as a branch of the art and science of healing.

While we must all cherish the hope that neurology will keep abreast of the great advances now going on in internal medicine and make its own significant contribution to human knowledge and welfare, there may well be differences of opinion as to how this is to be brought about.

At the present time, there are two causes for anxiety concerning the future of neurology:

1] The fiissiparous tendency shown of late. This may, unless it can be checked, well reduce this science to a number of unrelated and meaningless fragments which cannot survive in isolation.

2] The possibility that our outlook and our interest in research are not balanced and do not take adequate account of the many urgent problems in the study and control of nervous diseases that are our special responsibility. There is, therefore, urgent need for all the wisdom we can summon to the consideration of our subject.

What do we refer to when we speak of neurology, the future of which we are about to discuss?

The term has wide references, and some may include the morphology and physiology of the nervous system – its chemistry and physics. In a sense, it must include these branches of science insofar as they provide standards of the normal against which we assess the deviations wrought by disease and injury. Nevertheless, although an adequate knowledge of the normal is essential to us as physicians or surgeons, our primary concern and responsibility are with the abnormal – the morbid category. Anyone familiar with the dramatic history of medicine in the first half of the nineteenth century will realize how vital the concept of the morbid category is to us.

Unlike the pure anatomist or physiologist who pursues knowledge for its own sake, we pursue knowledge for a practical end: namely, the cure and prevention of disease. This is our first aim and responsibility, and it is subordinate to all else as long as we accept responsibility for the care of the sick and for the study of disease. It is, of course, the choice of any medical graduate to devote his life to the liberal study of any of the sciences basic to medicine, but, for the majority of members of this congress, this is not our situation. Our aim and our responsibility are to seek the causes and to study the nature of nervous disease so that we may gain control over it. In other words, if we are to lend precision to the term neurology, as it concerns us, we should call it a neuropathology.

Let me make it clear that this word is not to be used in its narrow and conventional sense as referring only to morbid anatomy and histology or to what we call clinical pathology; rather, I use it in its widest sense, including the study of the abnormal and of disease by all relevant modes of observation and by every resource of applied science that may serve our purpose.

I hope that I shall carry you with me in this definition of neurology because it lends a perspective to the diverse activities in which we engage. My definition of our science can logically be contrasted with the only other conceivable aspect of the science of neurology – the science of the normal nervous system. This includes its statics and dynamics, that is, its morphology and physiology – physiology being the discernment and rational for-

Chairman's address at Round Table Conference on the Future of Neurology at the First International Congress of Neurological Sciences, Brussels, July 27, 1957.

mulation of the dynamic properties of the organism.

I submit, then, that there are two neurologic sciences: the *science of the abnormal* and the *science of the normal*. It is not in question whether all our earlier meetings have been primarily and predominantly concerned with the science of the morbid category; this has never been a congress of anatomy and physiology.

It must be emphasized that I do not suggest that the study of the normal is no concern of ours; rather, it is my feeling that our primary responsibility is research into the abnormal. As men and women engaged in the practice of neurologic medicine or surgery, our first duty is to seek to unveil the secrets of disease. Research upon the normal is the primary function of university departments or institutes of anatomy and physiology.

This congress we have been attending is a congress of neuropathology, in the wide sense reiterated above. In its course, we have considered the science of the abnormal from many points of view and in the light of many methods of study. These include clinical observation and histologic, chemical, and physical laboratory investigations; methods have been derived from electronic engineering and from radiology, and, in the matter of diagnosis and treatment, we have the two broad divisions of medical and surgical technics. We have, in short, one science but many and diverse technics.

It is only from such a point of view that our activities fall into a coherent pattern, for, surely, what constitutes a science is a body of ordered knowledge rationally based and inductively derived. The term cannot possibly be applied to technics or handicrafts, however skilled their performance.

Because we have mistakenly elevated our technics to the status of sciences, we have succeeded in giving ourselves the illusion that the present congress has been one of several neurologic sciences. This, indeed, is what we have called it. It is my contention, however, that it has been a congress of one science, which, like every other biologic science, employs technics borrowed from the different physical sciences. These borrowings do not constitute separate neurologic sciences, and, except as constituents of neurologic science, they have no meaning. For example, what is the significance of morbid anatomy and histology when divorced from the study of disease in the living? What is the value of electroencephalography except in relation to disease in the living? In what sense do the various technics employed in these two different activities constitute them as independent sciences? In what possible sense can an organization devoted to the study of epilepsy represent a science distinguishable from neurology? I might go on to ask the same questions about the technics of radiology and of surgery.

These activities represent the different activities in which we engage when we pursue the one science of the abnormal nervous system — neuropathology — seeking to discover the causes and nature of disease and its cure and prevention.

In no other branch of medicine do we encounter this separatism, this splitting into fragments that do not represent independent sciences, each claiming to be as great as the whole. When cardiologists sit in congress, they do not speak of a congress of cardiologic sciences: clinical cardiology, cardiosurgery, cardioradiology, electrocardiography, cardiopathology, and so on. Nor is this passion for infinite fission found in the science of the normal nervous system. On the contrary, the trend toward integration is stronger than ever before. The research activities of anatomists and physiologists are scarcely distinguishable. Have we not learned that integration should keep pace with differentiation?

These are not merely academic questions or debating points. They pose a grave practical problem, the rational solution of which will determine the future of our science of neurology, that is, of neuropathology.

Whatever the approach of the individual to the study and treatment of nervous diseases, whether he seeks the solution of his particular problem in the clinic, the laboratory, or the operating theater, he owes allegiance to a single body of rational knowledge — the science of the nervous system in disease; in larger terms, the morbid category.

No one worker is intellectually independent of the results gained in other fields. We all need one another's contribution to the total store of knowledge. Each one of us depends

in some measure upon the skills of the laboratory, the operating theater, and the clinic that our various colleagues possess. No one of us can claim autonomy and the status of an independent science for his own particular aspect of neurologic knowledge or for his particular skill, art, or craft.

Our science of neurology, as I have defined it, is an indivisible whole, a seamless garment. If from unwisdom or apathy we allow its disintegration to continue, it will fall out of the main stream of advance in medical science and will lapse to the condition of a collection of technics not rationalized by a common body of ordered knowledge.

We need to look earnestly to our research responsibilities. The day is past when we can be content to make contributions to physiology and regard this as discharging our research responsibilities as physicians or surgeons. There are problems of disease that will never be solved by these academic activities and that need a dynamic experimental pathology. We have devoted too great a proportion of our human and material resources to such technics as electronic recording. The research worker who is tied to a single technic too often becomes a technician, with all the intellectual limitations this implies. He does not think in terms of problems but in terms of machines. The great scientists have never allowed this to happen to them.

■ With respect to *prognosis* in epilepsy, it may be observed, that in the cases where there is reason to suppose that the disease depends upon the compressing causes above, at large described, such as tumours, effusions, &c. acting mechanically and permanently on the brain, the case may be considered as almost hopeless. Boerhaave, Van Swieten, and several writers, as I before mentioned, have asserted that hereditary epilepsy is absolutely incurable. Hippocrates, however, says, that it is not less curable than other diseases if not of very long standing.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Neurology

BOOK REVIEWS

Liver-Brain Relationships

Ian A. Brown, 198 pp., Charles C Thomas, Springfield, Ill. $6.50.

The central core of this well-planned monograph is a systematic study of 42 patients with hepatic disease and coma and of 40 patients with hepatic disease without coma. A postmortem examination and thorough pathologic study of the brain and other systems of the body were made in the patients with coma.

The case material presents parenchymal liver disease and associated cerebral involvement. Particular emphasis is placed on hepatoencephalopathy with hepatic coma and on the responsible mechanism. Deranged ammonia metabolism secondary to liver failure is thought to be an essential biochemical factor. Numerous chemical reactions, however, participate in these involvements and it is the author's opinion that, in hepatic disease, no single substance can be incriminated as the cause of cerebral alterations, that the search for such a substance is futile, and that the elucidation of the problem awaits intensive biochemical study of enzymes, chromogens, bilirubins, cytochromes, and metals. Better tests of brain dysfunction and newer liver function studies are needed.

The neurologist may appreciate the well-selected data of an historical review of the liver-brain complex and, in particular, the concise description of the anatomy, physiology, and pathology of the liver. The listing of 29 functions of the liver is worthy of any physician's notebook or that of the senior medical student preparing for his National Board Examination.

The monograph is a fine example of the teamwork on the part of the biochemist, neurologist, and internist. It is aptly illustrated and adequately documented.

A. R. V.

The Peripheral Innervation

Emil Villiger's "Die Periphere Innervation." Eleventh edition, revised by Eugen Ludwig. 1957. Basel: Benno Schwabe & Company. 210 pages. $5.00.

THE NEWEST EDITION of Villiger's classic textbook of peripheral innervation has reached, in the hands of Professor Ludwig, the status of the most authoritative reference book on the subject. The material of the book is painstakingly and critically selected to serve a nonspecialist, as well as a neurologist in practice. Filtered through the sieve of 11 editions and illustrated with well constructed diagrams, the text is concise, direct, and easy to read, in spite of the dryness of the subject. Those who have even a modest reading knowledge of German will find it useful.

Having served several generations of practical physicians as a reference source for information on subjects notoriously difficult to retain, unless one is specializing in this particular clinical field, the book treats the sub-

ject in a manner which has proved its efficiency. In the first 22 pages, basic information on the finer structure of peripheral nerves and ganglia in the light of latest acquisitions of knowledge is discussed. In the following 20 pages a general review of the nerves and roots of the spinal cord and the autonomic nervous system is presented. This is followed by 45 pages of special description of topographic anatomy of spinal roots, plexuses, and nerve trunks and of the distribution of the sensory and motor somatic and sympathetic nerves. A 50-page section covers the subject of the cranial nerves. A section of 20 pages is dedicated to sympathetic and parasympathetic ganglia and plexuses. This exposition of the peripheral innervation is concluded with a 10-page discussion of the central sensory-motor and associative apparatus of integration. The concluding section of some 30 pages outlines the clinical implications and the differential diagnostic criteria of disturbances of peripheral and central innervation. There is also an index of subject matter.

P. I. Y.

Anatomies of Pain

K. D. Keele, 206 pp., Charles C Thomas, Springfield, Ill., 1957. $5.50.

This is an amazing monograph, presented in historical sequence, on the anatomy and physiology of pain. As might be expected, pain has been an object of speculation from the earliest times. It is to this historical viewpoint that the author brings a fine scholarship as he reviews the notions of pain in the Oriental literature, among the ancient Greek and Roman philosophers, among medieval writers, and among those of the modern era.

This treatise is a treasure-trove of lore, and some curious things that the reviewer had not known may be listed:

1] The ancient Egyptians, in embalming, chiseled through the left nostril, entered the cranial cavity through the ethmoids, and removed the brain through the opening. The brain was the only organ thrown away as waste! All the sensory and motor functions were ascribed to the heart and local blood vessels.

2] One-half of the world's population still believes that pain is related to the heart and blood vessels. A Pueblo Indian chief said: "White men think with the brain; that accounts for their shortcomings. Red men think with their heart."

3] Alcaman, a pupil of Pythagoras, was the first to assert that the brain, not the heart, is the seat of sensation and reason. Democritus, Anaxagorus, and Plato agreed, but Empedocles and Aristotle disagreed, maintaining that the heart was the seat of sensation. Diogenes worked out a compromise by putting the sensory center in the blood vessels of the brain – a view adopted by most writers of the Hippocratic school. Herophilus, immediately after Aristotle, dissected the body, described the difference between motor and sensory nerves, identified the brain as related to sensation and thought, and discovered that the most vital part of the central system was the medulla at the level of the calamus scriptorius, in effect recognizing the cardiac and respiratory centers.

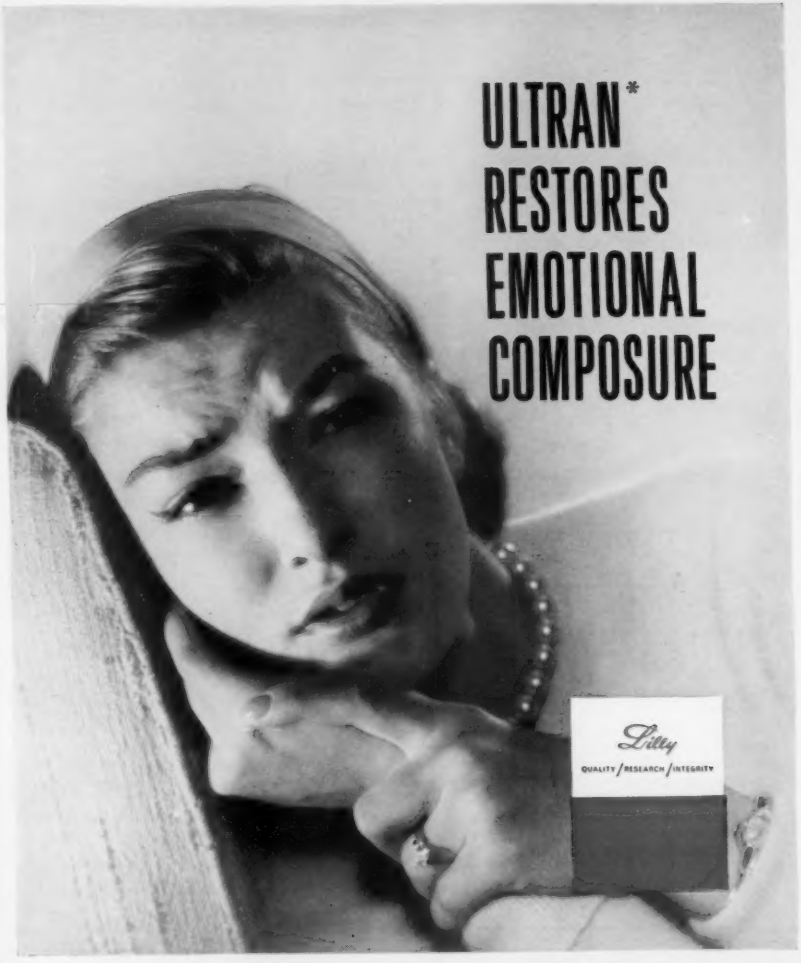
4] Galen, in the second century, revived the studies of Herophilus and reestablished the physiologic importance of the central nervous system. To the reviewer's surprise, Galen described the operative technics and the results of transverse section and of hemisection of the spinal cord. This work was repeated in 1860 by Brown-Séquard.

The modern era may very well have been introduced in the seventeenth century by Descartes, who placed the seat of maximum consciousness in the pineal body. His theories led to overaccentuating the dichotomy between psychologic and physiologic functioning, a view which continues to color and confuse our present-day attitude.

The treatise continues into the modern period. A particularly informative chapter on the discovery of the spinothalamic tract and an excellent summary of our present knowledge of pain pathways from periphery to sensory cortex with pertinent notes on diagnosis and medical and surgical treatment are presented.

This book is illustrated with well chosen figures of historical interest. Documentation appears to be thorough, and both subject and author indexes are provided.

A. R. V.



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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

OCTOBER 1958

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Augustus S. Rose, President-Elect
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Joseph M. Foley, Secretary
Charles Van Buskirk, Treasurer

AAN Membership Nearing 2,000 Mark

The total membership of the AAN is now almost 2,000; it may be 2,000 at this printing. Since August 31, 1958, a total of 71 physicians and scientists have been added to the membership roster. Among them are 5 Actives, 57 Associates, and 8 Junior members. The new members in all categories are: Joseph Abbiss, Gilbert L. Adamson, William P. Argy, Robert L. Bennett, Louis P. Britt, J. M. Casey, Burton Chance, Jr., Herbert G. Cohen, G. W. Cottrell, Peter G. Danis, George G. Deaver, Richard C. Deming, Charles G. Drake, William R. Duncan, Sven G. Eliasson, Arthur R. Elvidge, Eugene R. Elzinga, Howard A. Engle, Albert Ferguson, Jr., Frederick J. Fischer, Robert H. Fitzgerald, Paul T. Fukui, Gordon J. Gilbert, Harriet E. Gillette, Morris Goodman, Leon Greenspan, George P. Guibor, Francis M. Harris, Jr., Leonard Harris, Donald H. Harter, John E. Harvey, J. William Hillman, Ben L. Hull, Edward R. Kamen, Jose A. Keating, Donald C. Keyes, D. P. Kidron (Israel), Robert W. Kimball, David J. King, Fremont P. Koch, Leo J. Koven, Robert A. Kuhn, Walter Leslie, Harold B. Levy, Carl D. Martz, Campbell C. McCullough, Jr., Robert V. McMahon, A. Ziegler McPherson, Benjamin S. Meyer, William L. Minear, Livia H. Mitis, Joseph M. Moore, T. P. Morley, Charles I. Nadel, Dwight Parkinson, Roland Perkins, Winthrop M. Phelps, Manuel E. Pusitz, Hugo V. Rizzoli, Harold J. Rosen, Lester A. Russin, Jordan M. Scher, Lawrence Slobody, Henry A. Sloviter, Thomas L. Sooy, Alma Mary Stoiber, Gerald D. Timmons, Mary I. Tom, S. E. Turvey, Thomas W. Wallace, Adolfo Zier.... The total AAN membership is now 1,956, of which nine are Honorary, 52 Honorary-Corresponding, 773 Fellows and Actives, 786 Associates, and 336 Junior members.... Inquiries on AAN membership should be sent to Dr. Pearce Bailey, Chairman, AAN Membership Committee, National Institute of Neurological Diseases and Blindness, Bethesda 14, Md.

EPILEPSIA Reorganizes

Beginning early in 1959, EPILEPSIA, the official organ of the International League Against Epilepsy, will be published quarterly by the Elsevier Publishing Company, according to an announcement made by A. Earl Walker, Chairman, Committee on EPILEPSIA. Sir Francis Walshe will head the Editorial Board of the new journal and have with him as editors, Prof. Henri Gastaut of Marseille and Dr. Gilbert Glaser of New Haven, and as Secretary, Dr. Lorentz de Haas of Amsterdam

.... Scientific manuscripts may be submitted to either Prof. Gastaut, 149, Promenade de la Corniche, Marseille, VIIe, France or to Dr. Glaser, 333 Cedar Street, New Haven 11, Conn.

Forster Goes to Wisconsin

Francis M. Forster, President of the American Academy of Neurology and formerly Professor of Neurology and Dean of the Georgetown University School of Medicine has been appointed Professor and Chairman of the Department of Neurology at the University of Wisconsin School of Medicine.... The former Department Chairman, Hans H. Reese, will continue his professorship, but will relinquish his responsibilities as Department Chairman in order to devote his full time to research.... In his new post, Dr. Forster will direct an autonomous department of neurology with going residency training and research programs which are closely linked with activities in the basic neurologic sciences, especially in neurophysiology and neurochemistry.... The Georgetown Department of Neurology is now under the acting directorship of Desmond S. O'Doherty, formerly the number two man in that department.... In joining the "Big Ten," Forster will still pursue his interests on the national scene. In addition to being AAN President, he is Chairman of the AMA Section on Nervous Disease, and a member of the NINDB Council. When queried about his new appointment, Forster said, with a broad, twinkling smile: "This position offers a wonderful opportunity for development of a strong neurology department, closely related to the basic sciences."

Houston Symposium To Highlight Cerebrovascular Disease

A symposium on the pathogenesis and treatment of cerebrovascular diseases is the central theme of the Seventh Annual Scientific Meeting of the Houston Neurological Society (March 12-14, 1959). The program is an inclusive one which will be devoted to discussions of basic mechanisms and the diagnosis and treatment of cerebrovascular diseases, both medical and surgical. Its four major parts concern considerations of basic embryology and anatomy, the pathogenesis and physiologic mechanisms of occlusive disease, cerebral hemorrhage, and subarachnoid hemorrhage. Many of the country's leading authorities will participate in the symposium.... Inquiries should be addressed to Dr. William S. Fields, Professor and Head, Division of Neurology, Baylor University College of Medicine, Houston, Texas.

Neuropathology Training Program Enlarged at Langley Porter

A specialized training program for residents in general pathology and in clinical neurology has been organized at the Langley Porter Neuropsychiatric Institute in San Francisco, as a result of a grant to the University of California Medical School by the National Institute of Neurological Diseases and Blindness. Applications for traineeships in this program

should be sent to the Program Director, Dr. Nathan Malamud, Director of the Laboratory of Neuropathology, The Langley Porter Neuropsychiatric Institute, Parnassus and First avenues, San Francisco 22.

UCP To Consider the Problem of Hemiplegia

The 1958 annual scientific sessions of the United Cerebral Palsy will be devoted to an over-all critical evaluation of the problem of hemiplegia. The meeting is to be held under the auspices of the Society's Clinical Advisory Committee in the Mayflower Hotel, Washington, D. C. (November 15). The morning sessions, to be chaired by William Berenberg, will include opening remarks by H. Houston Merritt, the early recognition of hemiplegia (Meyer Perlstein), the pathology of hemiplegia (Webb Haymaker), measurement of motor handicaps in children (Schwartz and Zuck), neurosurgical approaches (Wilder Penfield and Russell Meyers), and orthopedic treatments (Lennox D. Baker, William T. Green, Winthrop M. Phelps, Robert C. Darling, and Svend M. Clemmesen of Copenhagen). The afternoon sessions, to be chaired by Pearce Bailey, will concern the problem of rehabilitation of the hemiplegia patient. Among the contributors are George G. Deaver, Chester W. Swinyard, Martin F. Palmer, Jon Eisensen, Charles B. Shields, Herman Yannet, Martin Moed, Howard A. Rusk, and Bronson Crothers .... The scientific sessions will be summarized by Brewster S. Miller, Medical Director, United Cerebral Palsy.

Foundation for Parkinson's Disease Makes Grant Awards

The newly formed Parkinson's Disease Foundation has announced the approval by its Research Advisory Board of five research grants to institutions and one fellowship stipend out of the $150,000 made available so far for this purpose. H. Houston Merritt is the Chairman of the Foundation's Research Advisory Board. Application forms for additional institutional grants or for postgraduate and undergraduate fellowships are now available at the Foundation headquarters in the Hotel Beverly in New York City.

Neurological Programs in Chile

The focus of neurologic and neurosurgical interest is being attracted to Santiago, Chile, where three international congresses and one international symposium are to be held (April 12-15, 1959). These meetings, sponsored by the government and the University of Chile, are the VIII Latin American Congress of Neurological Surgery (Prof. Dr. A. Asenjo, President), the IV South American Congress of Electroencephalography and Clinical Neurophysiology (Dr. A. Mosovitch, President), International Symposium on Frontiers in Neurology (Prof. A. E. Walker, President), and the First International Congress of Nursing in Neurosurgery.... The International Symposium on Frontiers in Neurology will be opened with a presiden-

tial address by A. Earl Walker on "Future of Research in Neurology." The topics of the program are ultrasonics by Ballentine (United States) and Leksell (Sweden); depth recording by Bates (England); cerebral circulation by Denny-Brown (United States) and Lazorthes (France); and the ultra structure of cortical neurones by Robertson (England) and Palay (United States). These presentations will be discussed by Fernandez Moran (Venezuela), Fuster (Uruguay), DeRobertis (Argentina) and Hakim (Colombia). During the congresses, didactic courses will be given by international authorities on subjects of special interest, selected from a panel of experts.... Headquarters for the meetings is the Instituto de Neurocirugia, Casilla 70-D, Santiago, Chile.

Briefs The 1958 annual meeting of the Chilean Society of Neurosurgeons (Professor Dr. Alfonso Asenjo, President), will be held in Santiago (September 12-13, 1958).... Brewster S. Miller, Director of Research, Research and Educational Foundation of the United Cerebral Palsy, announces that the Foundation has inaugurated three new training programs: Postdoctoral Fellowships in Brain Research, Clinical Fellowships in Cerebral Palsy for physicians and dentists, and a Medical Student Fellowship in Cerebral Palsy. Information may be obtained on these programs from the Research and Educational Foundation of United Cerebral Palsy, 321 West 44th Street, New York 36, New York.... The annual meeting of the Medical Advisory Board of the Myasthenia Gravis Foundation will be held December 12, 1958, at the Hotel Roosevelt, New York City. The Board will not hold scientific sessions at this meeting in order to concentrate on the organization of their International Symposium to be held in conjunction with the annual meeting of the AAN in Los Angeles in April 1959.... Edward W. Dempsey has been named Dean of the Washington University School of Medicine, effective September 1.... Chester A. Swinyard, former Medical Director of the Rehabilitation Center at the University of Utah College of Medicine, has been appointed Associate Director of the Children's Division of New York University-Bellevue Medical Center's Institute of Physical Medicine and Rehabilitation. Dr. Swinyard also has been appointed Research Consultant to the Association for the Aid of Crippled Children.

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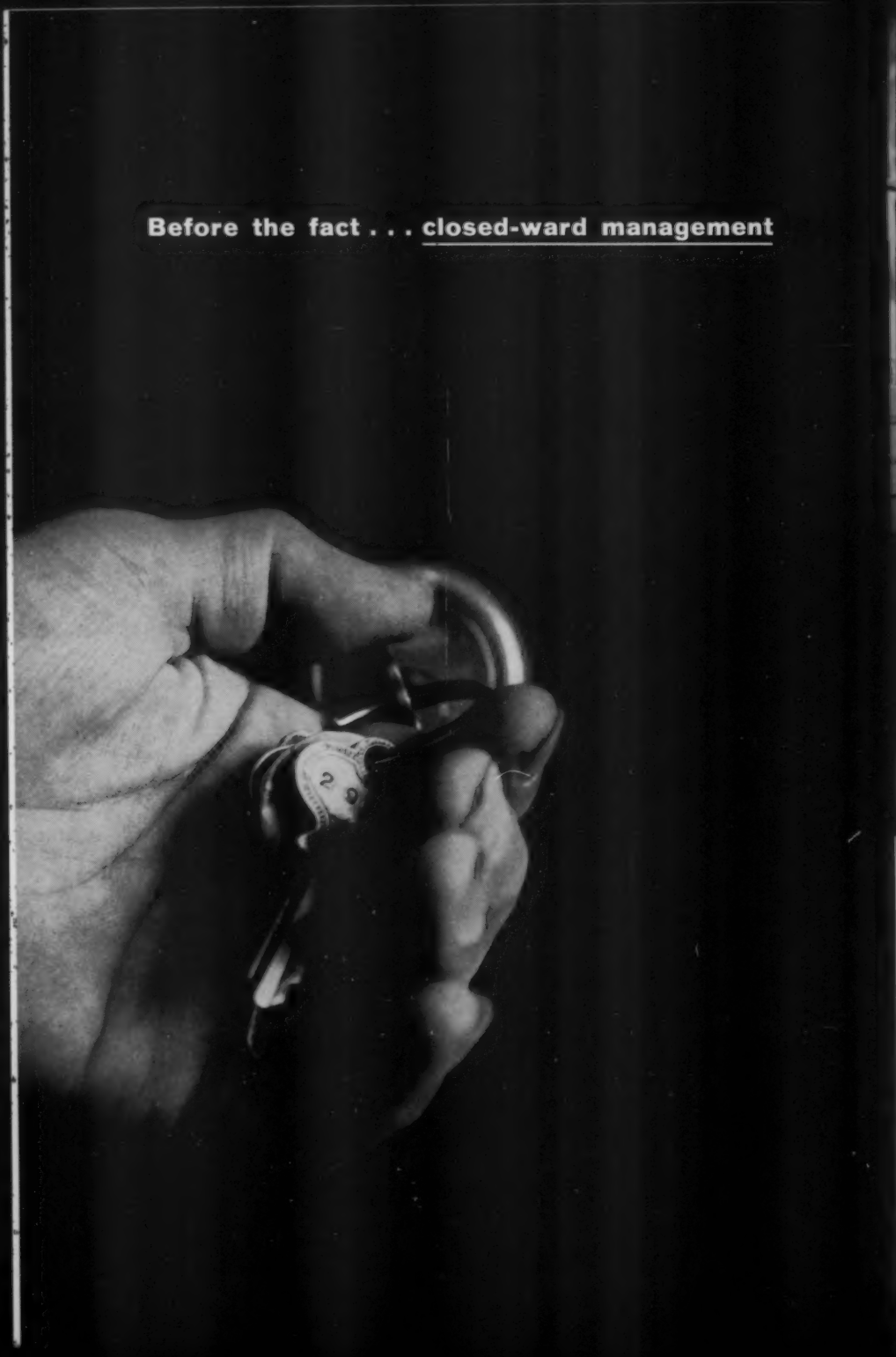
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1. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Emotional disorders treated with meprobamate and promazine. Connecticut M. J. 21:1047, Dec. 1957.

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by disease

DIAGNOSIS	NO. OF PATIENTS	NO. IMPROVED
SCHIZOPHRENIA		
PARANOID	7	2
NON-PARANOID	45	34
DEPRESSION		
PSYCHOTIC†	37	25
NEUROTIC	16	10
ANXIETY STATE	9	8
CHARACTER DISORDERS	15	13
OTHERS	16	13
TOTALS	145	105

by symptom

SYMPTOM	NO. IMPROVED
SLEEP DISTURBANCES	36
ANXIETY	30
TENSION	31
AGITATION	8
OTHERS	11
TOTAL	116

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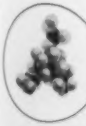

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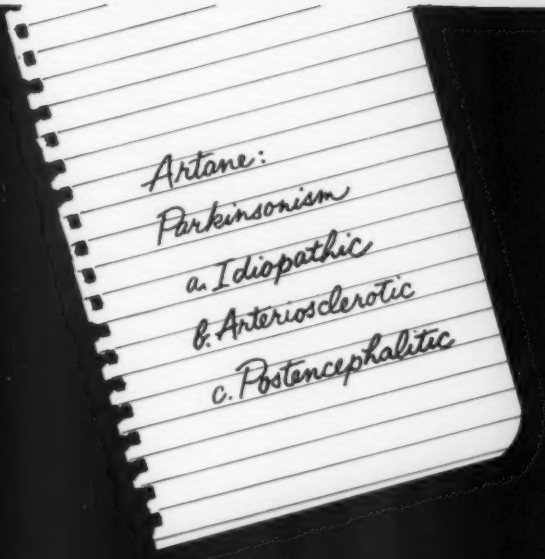

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